Alcohol Intake and Cardiovascular and Gastrointestinal Diseases

Do other factors matter?

Janne Schurmann Tolstrup
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This review is based on the following publications:


PREFACE

My interest in epidemiology started during my appointment as a research assistant at the Institute of Preventive Medicine in 2001. Here, the stimulating scientific environment under the direction of Thorkild IA Sørensen and Morten Grønbæk created basis for my first epidemiological training and interest. Later, at the National Institute of Public Health, my work became more focused on studying health effects of alcohol, a work that was carried out on the background of the alcohol epidemiological studies performed by especially Morten. I wish to thank Morten for an increasing number of years of fruitful and inspiring collaboration.

While preparing the papers for this thesis, I have had the opportunity to work with some excellent and creative persons (Anne Tjønneland, Berit Heitmann, Kenneth Mukamal, Kim Overvad, Majken Karoline Jensen, Søren Rasmussen, Thorkild IA Sørensen, Ulrik Becker). For this, I am grateful.

I thank Louise Kristiansen and Ulla Arthur Hvidtfeldt, talented former students of mine, who first-authored two of the papers for this thesis.

I am most indebted to Børge Nordestgaard for his continuous support in my scientific education. Børge is a role model in the performance of structured, scientific work and he seems able to glimpse the bigger picture of every complexity. Ulrik Becker is thanked for commenting on this thesis and for generously sharing his knowledge within alcohol and gastroenterology.

I wrote a major part of this thesis at San Cataldo, in the beautiful surroundings of the Amalfi coast. This can highly be recommended to anyone who wishes for concentration and peace, while being in the pleasant company of others.

Thanks to my colleagues at the National Institute of Public Health for contributing to an open and stimulating workplace.

I owe thanks to participants as well as to initiators of the cohort study included in this thesis, especially the Copenhagen City Heart Study and the Diet, Cancer and Health Study, who have generously made their data available for my work.

Finally, I wish to thank my family and friends for their never ending support and continuous interest in my research.
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ABBREVIATIONS
ADH alcohol dehydrogenase
ALDH acetaldehyde dehydrogenase
AF atrial fibrillation
ALT alanine aminotransferase
AST aspartate aminotransferase
CHD coronary heart disease
CI confidence interval
γ-GT γ-glutamyl transpeptidase
HDL high-density lipoprotein
IRD incidence rate difference
LDL low-density lipoprotein

Note: 1 drink corresponds to 12 grams of pure alcohol
1. INTRODUCTION

Alcohol drinking has been part of human civilization for millennia. It is used worldwide, and in most Western societies, nondrinkers constitute the minority. The level of intake is high, averaging 15 drinks per week for each adult European man and women (WHO 2004). For many, the use of alcohol is linked with pleasure and sociability, but its use potentially has harmful consequences; alcohol contributes substantially to the global burden of disease and 4% of all deaths are attributable to alcohol, more so among men than among women (6.3% vs 1.1%) (Rehm et al. 2009a). While this ranks alcohol high on the list of avoidable risk factors, alcohol in the context of public health is not as simple as is the case for instance tobacco smoking, where there seems to be no level of risk-free consumption and the risk of morbidity and mortality increases by every cigarette. In contrast, the association between alcohol and all-cause mortality is J-shaped; the nadir of the J reflects a relatively lower risk of coronary heart disease (CHD) among light to moderate drinkers compared with abstainers (Corrao et al. 2000) and the ascending leg of the J is reflecting an increased risk of alcohol-related diseases such as liver cirrhosis, pancreatitis, upper gastrointestinal cancers, cardiomyopathy, and polyneuropathy among excessive alcohol users.

The evidence that alcohol intake is causally related to a decreased risk of CHD is substantial and comprises abundant and consistent results from epidemiological studies in independent study populations, summarized elsewhere (Hill 2005; Rehm et al. 2003; Klatsky 2003; Maclure 1993), and experimental evidence from clinical trials of the biological mechanism through changes in lipids and haemostatic factors (Rimm et al. 1999). Further, none of the studies that have addressed various kinds of bias have left concerns about a non-causal explanation of the association between alcohol and CHD (Mukamal et al. 2001).

Hence, while the causality between alcohol and disease appears evident, several factors may influence the strength of alcohol’s effect, beneficial or harmful: the cardioprotective effect of alcohol may not apply to everybody or all circumstances and not all individuals who drink heavily develop alcohol-related diseases. Specifically, the effect of alcohol may depend on the drinkers’ age and sex, and on the pattern of which the alcohol is ingested; steady or binge. Other lifestyle habits, especially smoking, may be interacting with alcohol and cause a risk that differs in magnitude from what is expected from the risk associated with the individual exposures. Also, the risk of alcohol-related diseases may depend on certain genetic factors, especially genes that produce enzymes affecting the rate of alcohol degradation.

For the harmful effects, little research has been conducted into effects of modifying factors, maybe because the incidence of these diseases is lower than for CHD and hence the statistical power to perform stratified analysis is more limited. Further, the evidence of an association between alcohol and outcome stems to a large degree from case-control and clinical studies, and results obtained on the basis of general population cohorts are sparse.

While alcohol contributes to more than 60 types of disease and injury (Gutjahr et al. 2001), the focus in this thesis is on CHD, atrial fibrillation, liver cirrhosis and pancreatitis. With the ambition to improve the understanding of the individual impact on risk and thereby increase the possibility of primary prevention against alcohol-related diseases in the future, the aim is to review the data for differential effects of alcohol according to modifying factors on these diseases.

2. CARDIOVASCULAR DISEASE

An estimated 16.7 million or approximately 30% of global deaths result from various forms of cardiovascular disease. Of these, 43% are due to CHD (Mackay et al. 2004). Unlike liver cirrhosis and pancreatitis, the etiology of cardiovascular disease is multifactorial with several risk factors, including smoking, unhealthy diet, physical inactivity, hypertension and obesity. In contrast, moderate alcohol drinking is associated with a reduced risk of CHD. On the other hand, consumption of alcohol in excessive amounts may be associated with increased risk of atrial fibrillation.

Coronary heart disease

Consistently, a lower risk of CHD was observed in light and moderate alcohol drinkers in the Diet, Cancer and Health Study (Figure 1), the Copenhagen City Heart Study, and in each of the eight study cohorts of the Pooling Project of Diet and Coronary Disease (Hvidtfeldt et al. 2010; Tolstrup et al. 2009a; Tolstrup et al. 2006). The maximal benefit was obtained at around 1-2 drinks per day for women and 2-3 drinks per day for men; for higher amounts of alcohol intake, there seemed to be no further gain. Other studies have even reported an increase in risk at high intakes, indicating a J-shaped association between alcohol intake and CHD (Corrao et al. 2000).

Alcohol and cardiovascular biomarkers

The beneficial effect of alcohol is primarily thought to be mediated through an increase in HDL and a decrease in fibrinogen (Rimm et al. 2007; Mukamal et al. 2005a; Rimm et al. 1999; Langer et al. 1992; Criqui et al. 1987). For those biomarkers, we observed that increasing alcohol intake was associated
with increasing HDL cholesterol and decreasing fibrinogen with no threshold, i.e. even low amounts of alcohol intake were associated with increasing HDL and decreasing fibrinogen (Figure 2). These findings are consistent with the effects of alcohol intake in the low range on the risk of CHD. We also observed that alcohol intake at higher levels (>14/21 drinks per week for women/men) was associated with higher systolic and diastolic blood pressure and with increased levels of non-fasting triglycerides, which, on the other hand, are associated with increased cardiovascular risk (Nordestgaard et al. 2007; Lewington et al. 2002) and in support of a J-shaped association between alcohol and risk of CHD.

**Genetic variation in alcohol dehydrogenase**

Alcohol is passively absorbed from the stomach and duodenum and is distributed within the body's water compartment. The rate of alcohol degradation is 30 to 90 minutes per drink and it is influenced by sex, frequency of alcohol intake, age and genetic factors (Ramchandani et al. 2001). Alcohol degradation is mainly catalyzed by alcohol dehydrogenase (ADH), which is rate limiting for the reaction (Figure 3). At least 7 human loci encode alcohol degrading enzymes, of which class I (ADH1A, ADH1B and ADH1C) is characterized by enzyme products with high affinity for ethanol (subsequently referred to as alcohol), while other ADHs mainly degrade other types of alcohols (Osier et al. 2002). Functional genetic variation is found in ADH1B and ADH1C in vitro studies have shown that alleles ADH1B-2 and ADH1B-1 produce enzymes with a 40-fold difference in alcohol degradation rate, and alleles ADH1C-1 and ADH1C-2 produce enzymes with a 2.5-fold difference (Bosron et al. 1986) (Figure 4).

Despite the large difference in *in vitro* activity of the ADH1B-1 and ADH1B-2 enzymes, differences in alcohol degradation rate in human studies are modest and not even consistently observable (Neumark et al. 2004; Mizio et al. 1994). However, support for an *in vivo* effect comes from East Asian studies that consistently report that ADH1B fast metabolizers experience more unpleasant symptoms such as flushing when drinking alcohol compared with ADH1B slow metabolizers. A finding that probably can be attributed to the higher levels of acetaldehyde that are produced in individuals with fast alcohol degradation (Figure 3) (Yokoyama et al. 2003; Carr et al. 2002; Takeshita et al. 2001; Takeshita et al. 1996). Further, we found in 9,080 Caucasians that the ADH1B fast genotype was associated with a lower alcohol intake, which further supports a functional role of this variation (Tolstrup et al. 2007). For ADH1C, no effect on alcohol degradation rate was found in a human study (Whitfield 1994).

In Caucasians, frequencies of the most active alleles (ADH1B-2 and ADH1C-1) are 2% and 58%, much different from the allele distribution in East Asians where corresponding frequencies are 70% and 93% (Tolstrup et al. 2007; Zintzaras et al. 2006). Hence, most studies on ADH1B genotypes are conducted in East Asians and most studies on ADH1C genotypes are conducted in Caucasians. The fast alleles are in linkage disequilibrium, meaning the majority of individuals who are hetero- or homozygous for the fast ADH1B-2 will also be hetero- or homozygous for the fast ADH1C-1 genotype.

It has been suggested that slow metabolizers may have lower risks of CHD compared with fast metabolizers, because they have alcohol in the blood for a longer period of time. Findings in accordance with this hypothesis were obtained in the Physicians' Health Study, where moderate alcohol consumption was associated with a decreased risk. However, the ADH1C genotype modified this association: as compared with nondrinkers, the relative risk among ADH1C slow metabolizers who drank 8 or more drinks per week was much lower than among the ADH1C intermediate and fast metabolizers in the same alcohol category (p=0.01 for ADH1C-alcohol interaction) (Hines et al. 2001) (Table 1). In support of biological plausibility of this result, the plasma HDL level was significantly higher among the slow metabolizers. However, results from studies that followed, mainly of smaller size, were less convincing (Ebrahim et al. 2008; Heidrich et al. 2007; Younis et al. 2005; Djousse et al. 2005b) (Table 1). The ADH1B genotypes, which are very unevenly distributed among Caucasians, were

**Figure 2. Alcohol intake and level of cardiovascular biomarkers**

*P*-value for linear trend, **P**-value for trend for alcohol intake >21 drinks/week, **P**-value for U-shape. Data from the Copenhagen City Heart Study (modified from Tolstrup et al. 2009).

**Figure 3. Alcohol degradation**

ADH; alcohol dehydrogenase, ALDH; acetaldehyde dehydrogenase.

**Figure 4. The ADH gene cluster.** The ADH class I genes (ADH1A, ADH1B, ADH1C) have high affinity for ethanol. Genetic variation affecting enzyme activity is found in ADH1B and ADH1C (modified from Osier et al. 2002 and Bosron et al. 1988).
not accounted for in any of these studies. We retested the hypothesis in the Copenhagen City Heart Study; in this material, the power to detect an ADH1C-alcohol interaction of an effect size similar to that observed in the Hines et al. study was 97%.

However, we found no difference in the risk of myocardial infarction according to the ADH1C genotype among either light to moderate or heavy drinkers (Figure 5, p=0.49 for interaction) (Tolstrup et al. 2009a). Adjusting results for the ADH1B genotypes or, alternatively, excluding ADH1B fast metabolizers from the analysis had no influence on results. The statistical power to perform separate analyses for the ADH1B genotype was insufficient. Similar results were obtained from the Diet, Cancer and Health Study; there was no difference in the risk of acute coronary syndrome according to ADH1C genotype in strata of the amount or frequency of alcohol intake (Tolstrup et al. 2010).

We also tested whether ADH1B and ADH1C genotypes were independently associated with biomarkers of cardiovascular disease (systolic and diastolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides and fibrinogen) and whether associations between alcohol and the biomarkers were modified by genotypes, but found no evidence of either of the hypotheses: ADH1B and ADH1C genotypes were not consistently associated with any of the biomarkers among men or women, and there was no sign of interaction between genotypes and alcohol intake on any of the cardiovascular biochemical risk factors (all P-values >0.05) (Tolstrup et al. 2009a).

Taken together, the lower risk of CHD among light to moderate drinkers does not seem to be modified by the ADH1C genotype to any major extent. First, despite the quite strong interaction observed by Hines et al., later studies have not replicated this finding (Table 1). Second, other studies using biomarkers, mainly HDL, as outcome, are not demonstrating any modification between alcohol and ADH1C genotype on the level of the respective biomarker either (Tolstrup et al. 2009a; Ebrahim et al. 2008; Younis et al. 2005; Djousse et al. 2005a; Whitfield et al. 2003). Third, in vivo effects of ADH1C variations on the rate of alcohol degradation, demonstrating that individuals with ADH1C slow genotype are clearing alcohol more slowly than individuals with the faster genotype, have been difficult to assess in experimental studies (Whitfield et al. 2001; Whitfield 1994; Couzigou et al. 1991).

The power to detect interactions between genetic variations and environmental exposures increases steeply as the relative risks associated with either exposure approaches unity. The maximal effect of alcohol on the risk of CHD is about 0.7 (relative to nondrinkers), and the effect of the genotype in the absence of alcohol is expected to be null (since ADH genes have no known pleiotropic effects). In ours as well as the other studies, the statistical power to detect ADH1C-alcohol interactions on the risk of CHD was most likely insufficient. Hence, it cannot be excluded that the ADH1C genotypes play a minor role for the association between alcohol intake and CHD; a formal meta-analysis of the studies in Table 1 could maybe answer this question.

In conclusion, the importance of the ADH1B and ADH1C genotypes for the association between alcohol and the risk of developing CHD, if any, is limited.

### The influence of sex

For a given alcohol intake, blood alcohol levels will be higher for women than for men because women have smaller body sizes and relatively more body fat. This means that any dose of alcohol will imply a higher effective dose for women than for men, and women are, thus, generally more sensitive to any alcohol-related effect. Further, women differ from men in alcohol pharmacokinetics and in effects of alcohol on sex hormones (Register et al. 2002; Muntenhaler et al. 1999; Gavaler et al. 1993; Colditz et al. 1987).

In line with this, a meta-analysis by Corrao and coworkers indicate differences in the cardioprotective effect of alcohol between men and women (Corrao et al. 2000): in women, the measured risk of CHD decreased up to 6 drinks per week, showed evidence of protective effects up to 18 drinks per week, and reached statistical significance of harmful effects at 30 drinks per week. Conversely, the measured risk in men was

### Table 1. Summary of previous findings of ADH1C, alcohol and CHD

Presented numbers are relative risks (95% CI) compared with ADH1C-1/1 nondrinkers (for Ebrahim et al. incidence rates are presented). P represents P-value for the ADH1C-alcohol interaction.

*P*-value for alcohol-ADH1C interaction was 0.02 after post hoc regrouping alcohol into 1-2 and 2+ drinks per week (the corresponding risk estimates are not shown).

<table>
<thead>
<tr>
<th>Study</th>
<th>N events</th>
<th>Alcohol dr/wk</th>
<th>1/1 (fast)</th>
<th>ADH1C 1/2 (intermed.)</th>
<th>2/2 (slow)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolstrup et al. 2010</td>
<td>770</td>
<td>1-6</td>
<td>1 (reference)</td>
<td>1.38 (0.87-2.19)</td>
<td>1.10 (0.59-2.08)</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-20</td>
<td>0.88 (0.56-1.39)</td>
<td>0.97 (0.62-1.51)</td>
<td>0.91 (0.52-1.58)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>21+</td>
<td>0.97 (0.59-1.59)</td>
<td>0.73 (0.45-1.19)</td>
<td>0.84 (0.46-1.54)</td>
<td></td>
</tr>
<tr>
<td>Tolstrup et al. 2009a</td>
<td>628</td>
<td>1-13</td>
<td>0.99 (0.70-1.40)</td>
<td>0.98 (0.71-1.37)</td>
<td>0.83 (0.55-1.25)</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14+</td>
<td>0.80 (0.53-1.23)</td>
<td>0.82 (0.56-1.19)</td>
<td>0.88 (0.55-1.42)</td>
<td></td>
</tr>
<tr>
<td>Ebrahim et al. 2008</td>
<td>145</td>
<td>3-23</td>
<td>7.9 (5.2-12)</td>
<td>6.2 (4.2-9.1)</td>
<td>11.3 (7.1-18)</td>
<td>0.19</td>
</tr>
<tr>
<td>Heidrich et al. 2007</td>
<td>72</td>
<td>1-8</td>
<td>0.56 (0.19-1.61)</td>
<td>0.83 (0.34-2.07)</td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8+</td>
<td>1.06 (0.50-2.25)</td>
<td>0.36 (0.16-0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younis et al. 2005*</td>
<td>220</td>
<td>1-5</td>
<td>0.70 (0.40-1.21)</td>
<td>0.56 (0.32-0.99)</td>
<td>0.66 (0.31-1.38)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5+</td>
<td>0.57 (0.33-0.98)</td>
<td>0.77 (0.47-1.26)</td>
<td>0.68 (0.36-1.27)</td>
<td>0.49</td>
</tr>
<tr>
<td>Djousse et al. 2005</td>
<td>132</td>
<td>&gt;0</td>
<td>0.74 (0.41-1.32)</td>
<td>0.60 (0.34-1.08)</td>
<td>0.53 (0.24-1.18)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hines et al. 2001</td>
<td>395</td>
<td>1-8</td>
<td>1.11 (0.67-1.84)</td>
<td>0.66 (0.40-1.08)</td>
<td>1.02 (0.55-1.88)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8+</td>
<td>0.62 (0.34-1.13)</td>
<td>0.68 (0.40-1.15)</td>
<td>0.14 (0.04-0.45)</td>
<td></td>
</tr>
</tbody>
</table>

[Figure 5. Relative risk of CHD according to ADH1C genotype and alcohol intake in men and women](from Tolstrup et al. 2009a).
decreasing up to 15 drinks per week, showed evidence of protective effects up to 51 drinks per week and reached statistical significance of harmful effects at 67 drinks per week. Hence, both the protective and the detrimental effects of alcohol on CHD are achieved at lower levels in women than in men.

**Does the effect of alcohol on CHD depend upon age?**

CHD etiology in young adults may differ from that of older individuals; for instance, relatively more cases of CHD among younger adults can be attributed to genetic causes (Zdravkovic et al. 2002; Marenberg et al. 1994). Hence, this age group may not benefit from alcohol drinking as much as older individuals. Since the incidence of CHD is very low in men younger than 40 years and in women younger than 50 years, the statistical power to compare effects of alcohol in different age strata is insufficient in most data sets. By using pooled data from eight cohort studies from North America and Europe, the Pooling Project on Diet and Coronary Disease, we tested if associations between alcohol and CHD in young adults (39-50 years), middle-aged (50-60 years) and older individuals (60+ years) were similar (Hvidtfeldt et al. 2010). Overall, associations between alcohol intake and CHD risk seemed similar by age group (Figure 6, left panel). This visual impression was confirmed by a statistically nonsignificant test for interaction (P=0.25 for men and 0.34 for women). In all age groups, a lower CHD incidence was observed among moderately drinking men and women than among nondrinkers. However, a smaller CHD incidence rate difference (IRD) between nondrinkers and moderate drinkers was observed among younger men (IRD=45 per 100,000; 90% CI: 8-84) than among middle-aged (64 per 100,000; 24-102) and older men (89 per 100,000; 44-140) (Figure 6, right panel). Among women, similar results were obtained.

The association between alcohol and CHD risk across age groups is sparsely studied. In the Honolulu Heart Program, including 18,456 men, authors observed a lower risk among drinkers aged 45-74 years as compared with nondrinkers; among older men (75+ years) there was no difference in risk between drinkers and nondrinkers (Abbott et al. 2002). Hence, authors concluded that the association between alcohol intake and CHD risk attenuated with age, which is somewhat in contrast to the findings from the Pooling Project on Diet and Coronary Disease even though the 75+ year-olds were not analyzed separately.

Age is associated with drinking pattern; for instance, young people tend to binge drink more often than older individuals. Among Australians, the highest proportion of those with occasional heavy drinking was found among the young men and women (18-24 years old); with increasing age, this proportion decreased continuously over the entire age span (Livingston et al. 2009). This is similar to findings in the United States, where frequent heavy drinking comprised 27% of 18- to 29-year-old men and only 4% of 65+ year-olds (Hilton 1987). The Pooling Project on Diet and Coronary Disease did not include drinking pattern, which is a limitation of the results. However, if the youngest participants binge drink more often than older participants, their risk is probably conservatively estimated because binge drinking does not seem to be associated with a decreased risk of CHD.

In conclusion, young adults, middle-aged and older individuals seem to have the same relative effect of alcohol intake on CHD risk. So even though the etiology of CHD may differ according to age, this indicates that the mechanism through which alcohol seems to protect against CHD also applies for young adults. However, younger adults are at low risk of CHD and the absolute beneficial effect is small.

**The influence of drinking pattern**

In epidemiologic studies where alcohol exposure is summarized into a single measure of average amount, individuals who drink small amounts on a number of weekdays are categorized with individuals who drink the same weekly amount on a Saturday night. Evidence has emerged that these evidently dissimilar drinking patterns are associated with different risks of morbidity and mortality.

Drinking pattern has been defined in various ways such as drinking with meals, in weekends only, to intoxication, to a
certain blood alcohol level, more than a certain amount per session (6 drinks, 13 drinks, \( \frac{1}{2} \) a bottle of spirits, etc.), and amount and frequency have been combined. A common feature of these approaches is that alcohol exposure is described in more than one dimension. Thus, in these studies the main focus is not to compare nondrinkers and drinkers, but rather to compare drinkers characterized by different drinking patterns.

In the Diet, Cancer and Health Study, we compared mortality risk among participants with different drinking frequencies. We found that the risk was higher among women drinking 7 drinks per week and among men drinking 14 drinks per week if this amount was taken on one day of the week compared with distributing the same amount on more days of the week (data not shown) (Tolstrup et al. 2004). In other studies, results consistently imply an increased mortality risk of drinking large amounts of alcohol per session (Makela et al. 2005; Laatikainen et al. 2003; Malyutina et al. 2002; Rehm et al. 2001; Trevisan et al. 2001).

Some of the excess mortality risk that is associated with a binge-like drinking pattern seems to be due to an increased risk of CHD. In the Male Health Professionals, Mukamal and coworkers showed that the risk of CHD seemed to be more strongly related to frequency than to amount of alcohol intake among men (Mukamal et al. 2003). In the Diet, Cancer and Health Study, we observed similar results for the men: relative risks were generally lowest for the most frequent intake within similar categories of amount (Table 2). For example, among men drinking on average 7-13 drinks per week, relative risks of CHD were 0.89 (95% CI: 0.62-1.29) for drinking alcohol on \( \leq 1 \) days per week, 0.81 (95% CI: 0.67-0.98) for 2-4 days a week, and 0.66 (95% CI: 0.52-0.83) for 5-7 days per week (\( P \) for trend = 0.0001). For the same category of drinking frequency, relative risks for increasing amount of alcohol intake tended to be similar. Among women, the tendencies in results were opposite; it seemed that amount was more strongly associated with CHD risk than frequency among women (Mukamal et al. 2005a). The statistical power among women was lower than among men, and results in women should, therefore, be taken with caution.

Most studies trying to separate the effect of occasions of heavy drinking from the effect of the average alcohol intake found independently increased risk of CHD among both men (Trevisan et al. 2004; Laatikainen et al. 2003; Murray et al. 2002; Malyutina et al. 2002) and women associated with binging (Dorn et al. 2007; Laatikainen et al. 2003; Murray et al. 2002; Hammar et al. 1997). Furthermore, in a meta-analysis, the dose-response relation between alcohol intake and CHD risk was significantly different in irregular and regular drinkers; in irregular drinkers who consumed alcohol for 2 days a week or less often, a J-shaped curved was obtained, with an increasing risk at intakes over 11 drinks per week. In contrast, in regular drinkers who consumed alcohol on 3 days of the week or more often, a protective effect was observed, even at high amounts of alcohol intake (Bagnardi et al. 2008). This result is based on pooled data from two studies only (Tolstrup et al. 2006; McElduff et al. 1997) and should, thus, be taken with caution. Furthermore, sex-specific effects were not accounted for. Nevertheless, should this finding represent causality, difference in drinking pattern by study population can explain why some studies report an increased risk of CHD at high intake of alcohol (a J-shaped curve), while others find no increase in risk with increasing intake (sometimes referred to as L-shaped).

In conclusion, drinking pattern has independent effects on CHD risk. Data suggest that drinking frequency is inversely and independently associated with risk of CHD, at least among men. On the other hand, occasional heavy drinking (binge drinking) is associated with increased CHD risk.

### Is wine more healthy than beer and spirits?

It has been suggested that wine drinking has an especially beneficial effect – an idea that originated from the observation that the incidence of CHD in France was low despite a high prevalence of smoking and fat intake, the so-called French paradox (Criqui et al. 1994; Renaud et al. 1992). Biological explanations for a more cardioprotective effect of wine compared with beer and spirits include the fact that substances in wine (besides the ethanol) have been shown to inhibit platelet aggregation and to slow down oxidation of low-density lipoprotein (Ramprasath et al. 2010; Pace-Asciak et al. 1996; Renaud et al. 1996; Pace-Asciak et al. 1995; Frankel et al. 1993). In support of this appealing theory, it was found in the Copenhagen City Heart Study, that wine drinkers had a much lower mortality than beer and spirit drinkers (Grønbæk et al. 1995).

However, quite some evidence indicates that the apparent favorable effect of wine is an artifact resulting from characteristics of the drinker rather than of the drink itself. First, in an overview of 10 cohort studies most of them did not demonstrate a more pronounced cardioprotective effect of red wine compared to other beverages (Rimm et al. 1996). Differences in results from country to country according to wine, beer and spirits may be attributable to socio-economic or behavioral characteristics of wine, beer and spirits drinkers. In line with this studies have shown that wine drinkers are more likely to report optimal health, score higher in intelligent tests and to eat a more healthy diet than beer and spirits drinkers (Johan-

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**Table 2. Relative risks of CHD as a function of amount and frequency of alcohol intake.** Reference group. Data from the Diet, Cancer and Health Study (modified from Tolstrup et al. 2006).

<table>
<thead>
<tr>
<th>Amount (drinks/week)</th>
<th>Frequency (days/week)</th>
<th>( P ) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \leq 1 )</td>
<td>2-4</td>
</tr>
<tr>
<td>Men</td>
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<td></td>
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<tr>
<td>1-6</td>
<td>1.00*</td>
<td>0.80</td>
</tr>
<tr>
<td>7-13</td>
<td>0.89</td>
<td>0.81</td>
</tr>
<tr>
<td>14-20</td>
<td>1.10</td>
<td>0.91</td>
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<tr>
<td>21+</td>
<td>1.00</td>
<td>0.67</td>
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<tr>
<td>( P ) for trend</td>
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<tr>
<td>Women</td>
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<tr>
<td>1-6</td>
<td>1.00*</td>
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<td>7-13</td>
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<td>( P ) for trend</td>
<td>0.002</td>
<td>( \text{&lt;0.0001} )</td>
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In conclusion, some studies support the clinical and experimental suggestions of an effect of wine in addition to a light to moderate alcohol intake on cardiovascular disease, although the differences may be small and to a large extent may be due to confounding.

Atrial Fibrillation

Anecdotal evidence proposes that acute high doses of alcohol can trigger atrial fibrillation (AF) in otherwise cardiac-healthy individuals, a syndrome known as holiday heart and first described by Ettinger, and later supported by others (Thornton 1984; Lowenstein et al. 1983; Ettinger et al. 1978). Further, while AF in individuals younger than 45 years is rare, an alcoholic binge can cause this (Krishnamoorthy et al. 2009; Koul et al. 2005). The relationship of habitual alcohol intake with risk of incident AF is less certain.

Is the risk of AF according to alcohol threshold-shaped?

In at least four case-controls studies, the risk of AF was significantly increased among the most heavily drinking patients, while the risk associated with moderate drinking was comparable to abstinence (Djousse et al. 2004; Riuigomez et al. 2002; Koskinen et al. 1987). In the Copenhagen City Heart Study, we studied prospectively the association between alcohol and incident atrial fibrillation among 16,415 men and women; a total of 1,071 AF cases occurred during follow-up (Mukamal et al. 2005b). Among men, alcohol intake throughout the moderate range was not associated with risk of atrial fibrillation, but consumption of 35 or more drinks per week was associated with a relative risk of 1.45 (95% CI: 1.02-2.04). No increased risk was observed among moderately drinking women (Figure 7). In accordance with this result, in the Women’s Health Study, the risk of AF was not increased among women drinking up to 18 drinks per week; at higher amounts, the relative risk was 1.60 (95% CI: 1.13-2.25).

The above results all indicate a threshold-shaped association between habitual alcohol intake and AF risk; no increased risk at light to moderate intakes and an increased risk only at a certain level. In the Copenhagen City Heart Study, to explore this hypothesis further we used linear spines; the risk of AF increased notably at a threshold of >35 drinks per week, with a flat relationship at lower levels of intake.

In contrast to the above results, an analysis of the Diet, Cancer, and Health cohort found 25% to 46% higher risks of AF associated with average intake of just >12 drinks per week. However, no increased risk was observed among women at any intake (Frost et al. 2004). In two different cohorts of 65+ year-old men and women, no increase and inverse association, respectively, were found in the risk of AF according to alcohol intake (Mukal et al. 2007; Psaty et al. 1997). In both these populations, the level of alcohol use was low and binge drinking was uncommon; hence these results are not necessarily in contrast to the idea of a threshold-shaped association between alcohol and AF risk.

Heavier drinkers could sustain a higher risk of AF by different mechanisms. We assessed a series of potential mediators of the association of heavy alcohol intake with risk of AF, including blood pressure, incident CHD during follow-up, and incident congestive heart failure during follow-up. As expected, all three were strongly and independently associated with risk of AF. However, adjustment for these factors had little effect on the alcohol AF association. For example, the relative risk of AF among men who consumed 35 or more drinks per week was 1.45 in the basic model and 1.63 (95% CI: 1.15-2.31) with adjustment for all three potential mediators, indicating that these factors do not mediate to any major extent the relation between alcohol and AF (Figure 7). Other plausible explanations include the fact that chronic heavy alcohol use itself has toxic effects on the pericardium, as supported by animal studies (Piano et al. 1999), or chronic heavy drinking could have direct proarhythmic effects; explanations that can be further addressed in experimental studies. Third, heavier drinkers are likely to have repeated exposure to episodic heavy drinking (ie. binge drinking), which could increase the risk of triggering a single episode of AF. Difference in drinking pattern could potentially explain the difference in level of thresholds among the various studies; in study populations where the habit of heavy drinking occasions is common, the observed threshold in amount of alcohol intake will be lower than in study populations were binge drinking is rare. We found no clear evidence that drinking frequency was independently related with risk (data not shown). We did not have information on other dimensions of drinking pattern to perform further tests.

In conclusion, most studies have shown that moderate alcohol drinking is unrelated with risk of AF among men and women, while more heavy consumption is associated with a higher AF risk. This relationship does not appear to be related to the adverse effects of heavy drinking on CHD or blood pressure.

![Figure 7. Alcohol and risk of atrial fibrillation among men and women.](image-url)

White dots represent multivariate adjusted relative risks; black dots represent relative risks that are further adjusted for potential mediators (use of blood pressure medication, systolic blood pressure and incident diagnoses of CHD and congestive heart failure). Data from the Copenhagen City Heart Study (modified from Mukal et al. 2005).
3. GASTROINTESTINAL DISEASE

Liver cirrhosis and pancreatitis are generally considered to be the major alcohol-related diseases of the gastrointestinal tract. The impact of alcohol on cirrhosis morbidity and mortality has been scientifically recognized for decades. In populations where hepatitis infections are uncommon, ~80% of cirrhosis cases are attributable to excessive alcohol consumption, constituting 16% of deaths attributable to alcohol worldwide (Rehm et al. 2009a).

As early as 1878, alcohol was proposed as a risk factor for pancreatitis (Friedrich 1878), which has been confirmed in clinical series (Voiron et al. 1980; Sarles et al. 1979; Edlund et al. 1968), and it is well known that a large fraction of pancreatitis cases is caused by alcohol. However, epidemiologic studies on the quantitative aspect of the association between alcohol intake and pancreatitis have until recently been sparse, which is why the impact of alcohol induced pancreatitis on global morbidity and mortality has not been estimated (Rehm et al. 2009a; Rehm et al. 2009b).

Liver cirrhosis

Excessive alcohol intake associates with biochemical signs of liver damage and with liver disease, which has mostly been demonstrated in case-control studies (Corrao et al. 2004). Whether this is also the case for low to moderate levels of alcohol intake in individuals in the general population is less certain. Liver cirrhosis may take several years to develop; intermediate states from pathologically healthy organ to manifest disease exist in all ranges, but are often difficult to study in the general population because clinical symptoms have not yet arisen. Biomarkers for liver damage are appealing alternatives, since they are immediate and sensitive measures, objectively evaluating the current state of the organ.

Alcohol and biomarkers for liver damage

Extreme levels of alanine aminotransferase (ALT), albumin, alkaline phosphatase, bilirubin, coagulation factors II, VII and X, γ-glutamyl transeptidase (γ-GT) and mean erythrocyte volume are generally indicative of acute liver damage and are used routinely for clinical purposes (Burtis et al. 2006; Marks et al. 2002). Among participants of the Copenhagen City Heart Study 1991-94 and 2001-03, these biomarkers were obtained as part of the clinical examination. By combining the biomarker levels with questionnaire information of the participants’ self-reported alcohol intake, we found that increasing alcohol intake associated with increasing levels of ALT, γ-GT, albumin, bilirubin, coagulation factors and erythrocyte volume, and with decreasing levels of alkaline phosphatase (Tolstrup et al. 2009b) (Figure 8). As illustrated, the difference in levels of the various biomarkers between low, moderate, and excessive alcohol intake were mostly small and probably not indicative of subclinical liver damage; however, mechanistically it is nevertheless an interesting finding that biomarkers were influenced at low intakes of alcohol with no apparent threshold effect. These biochemical tests have not previously been correlated with usual alcohol intake in a large population sample.

It was somewhat surprising that alcohol associated with increased levels of coagulation factors II+VII+X, equivalent to decreased prothrombin time. Chronic damage of hepatocytes by alcohol usually leads to reduced capacity to produce proteins, as seen in alcoholic liver cirrhosis, while in less severe forms of alcoholic liver disease, prothrombin time and, thus, levels of coagulation factors II+VII+X may not be affected (Burtis et al. 2006; Marks et al. 2002). However, our observation agrees with previous epidemiological data which demonstrate that heavy alcohol consumption leads to a more procoagulant state with higher levels of coagulation factor VII (Lee et al. 2003). Alternatively, since albumin also increased in response to increasing alcohol intake, the mechanism behind the increased levels of coagulation factors may be yet unknown.

The increased levels of ALT, γ-GT, mean erythrocyte volume, and bilirubin in individuals with the highest alcohol intake observed in the present study are in accordance with those expected, that is, increased alcohol intake associates with increased biochemical signs of liver cell damage.

In conclusion, we observed that increasing alcohol intake from none through moderate and excessive intake leads to stepwise increasing signs of liver damage with no threshold effect. The mechanism behind some of these findings is not yet understood.

Alcohol and liver disease

As expected, increasing amount of alcohol intake was strongly associated with increasing risk of alcoholic liver cirrhosis and with a risk of alcoholic liver disease overall. The highest risk was observed among the most heavily drinking participants: as compared with nondrinkers, the risk of alcoholic liver cirrhosis was 13 (95% CI: 4.6-37) and the risk of alcoholic liver disease overall was 4.1 (95% CI: 2.5-7.0) for drinking more than 28 drinks per week (both P’s for trend<0.0001).
ADH genotypes, biomarkers and liver disease

Production of toxic acetaldehyde within cells is thought to be one of the causes of liver damage and disease in response to alcohol intake (Witt et al. 2007; Adachi et al. 2005; Lieber 2004). The ADH1B and ADH1C genotypes could lead to different intracellular acetaldehyde concentrations in response to alcohol intake, and thus to differences in damage and disease of the liver (Zintzaras et al. 2006; Cichoź-Lach et al. 2006; Sun et al. 2005; Verlaan et al. 2004; Matsumoto et al. 1996). We tested this hypothesis in the Copenhagen City Heart Study.

ADH1B and ADH1C genotypes were not associated with any of the biomarkers for liver damage (ALT, albumin, alkaline phosphatase, bilirubin, coagulation factors II, VII and X, γ-GT and mean erythrocyte volume), nor did ADH1B and ADH1C genotypes interact with alcohol on the level of any of these biomarkers (all P-values >0.05) (data not shown). Further, ADH1B and ADH1C genotypes were not associated with a risk of alcoholic liver disease, nor was the association between alcohol intake and liver disease modified by ADH1C genotype (Figure 9); we did not have enough statistical power to stratify similarly for ADH1B genotype.

This study and most other studies (Zintzaras et al. 2006) have not been able to demonstrate any effect of ADH1B and ADH1C genotypes on the risk of alcoholic liver disease. Also, in support of this finding, we could not even demonstrate an influence of these genotypes on biomarkers of liver damage in individuals in the general population.

In conclusion, ADH1B and ADH1C genotypes are not associated with alcoholic liver damage or disease.

Acute and chronic pancreatitis

The distinction between acute and chronic pancreatitis is not clear and disagreement as to whether they really are distinct diseases or whether repeated attacks of acute pancreatitis eventually lead to chronic pancreatitis exists (Apte et al. 2005; DiMaggio et al. 2005). The most common causes of pancreatitis are thought to be gallstones and excessive alcohol intake.

Alcohol, drinking pattern and pancreatitis

In case-control and clinical studies, patients with pancreatitis are found to have a higher alcohol intake (Yadav et al. 2009; Lin et al. 2001; Talamini et al. 1999; Yen et al. 1982; Durbec et al. 1978). Knowledge of the quantitative association between alcohol drinking habits in the general population is sparse. To assess the association between amount, type and frequency of alcohol intake and risk of pancreatitis, we used data on 17,905 men and women in the Copenhagen City Heart Study. A high alcohol intake was similarly associated with a risk of both acute and chronic pancreatitis for men and women (Kristiansen et al. 2008). The risk of total pancreatitis increased with increasing alcohol intake, but was, however, only statistically significant above 35 drinks per week (Figure 10). To test for a threshold-like relationship, we remodeled the association between alcohol and pancreatitis using fractional polynomials; however, results did not indicate a threshold. The curves flattened out at high intakes, but the test for linearity did not provide evidence for departure. The relative risk of total pancreatitis increased with 1.13 for every additional drink per day (95% CI: 1.06-1.21). In a recent metaanalysis, the corres-

![Figure 9. Alcohol intake and risk of alcoholic liver disease by ADH1C genotype. *Reference group. Data from the Copenhagen City Heart Study (from Tolstrup et al. 2009).](image)

![Figure 10. Alcohol and risk of pancreatitis](image)
seem to be associated with independent risks, but this calls for further research on the subject.

**Smoking – an independent risk factor for pancreatitis?**

In the medical literature, smoking is generally not mentioned as a preventable cause of pancreatitis, even though quite a few, mostly case-control, studies suggest this (Law et al. 2010; Yadav et al. 2009; Lindqvist et al. 2008; Morton et al. 2004; Lin et al. 2008; Talamini et al. 1999; Talamini et al. 1996; Bourliere et al. 1991; Lowenfels et al. 1987; Yen et al. 1982). Also, evidence from experimental studies suggest that smoking is associated with pancreas damage (Wittel et al. 2008; Wittel et al. 2006; Doi et al. 1995; Chowdhury et al. 1995). In most populations, smoking is strongly associated with alcohol drinking, and an independent effect of smoking can be difficult to assess, especially from a case-control design. We aimed at assessing the independent effects of smoking on the risk of pancreatitis in the general population.

In the Copenhagen City Heart Study, we observed dose-response associations between smoking and risk of acute and chronic pancreatitis in men and women (Tolstrup et al. 2009c). For total pancreatitis, the relative risk as compared with never smokers was 2.5 (95% CI: 1.5-3.9) and 3.3 (95% CI: 1.9-5.8) for men and women who smoked 15-24 and ≥ 25 grams of tobacco per day (Figure 11). For former smokers, we found a statistically significantly increased risk of pancreatitis (1.7, 95% CI: 1.0-2.7). This relatively high risk in the ex-smokers did not seem to be due to sick-quitters because omitting the first years of follow-up had only limited effect on the size of the hazard ratio. Lung function within smoking categories ranged in the expected order (decreasing in the order ofnever-smokers, ex-smokers, and current smokers of 1-14, 15-24 and >25 g/day, respectively). Also, the amount of carbon monoxide in the expired air was similar among never and ex-smokers, which indicates that there was not a substantial fraction of current smokers that was misclassified as ex-smokers. We did not have sufficient statistical power to further explore the risk among the ex-smokers.

We performed additional analyses to explore if the risk of pancreatitis associated with smoking was independent of alcohol: first, the association between smoking and pancreatitis was confirmed among consistent light-to-moderate alcohol drinkers (participants who in each of the examinations of the Copenhagen City Heart Study reported to drink maximally 14 drinks per week for women and 21 drinks per week for men), and second, the association between smoking and the risk of pancreatitis was stratified according to alcohol intake at the examination closest to the pancreatitis diagnosis (Figure 12).

![Figure 11. Smoking and risk of pancreatitis](image1)

**Figure 11. Smoking and risk of pancreatitis**

Data from the Copenhagen City Heart Study (modified from Tolstrup et al. 2009c).

![Figure 12. Alcohol intake, smoking status and risk of pancreatitis](image2)

**Figure 12. Alcohol intake, smoking status and risk of pancreatitis**

*Reference group. Data from the Copenhagen City Heart Study (from Tolstrup et al. 2009).

An increased risk of pancreatitis with increasing amount of smoking was consistently observed in both analyses. There was no evidence of interaction between alcohol and smoking on the risk of pancreatitis (P =0.70).

Approximately 46% of cases of pancreatitis were attributable to smoking in this cohort with a high proportion of current and former smokers (only 38% were never smokers). During the last decade, the proportion of smokers in the Danish population, as in most Western populations, has decreased, so the etiologic fraction of pancreatitis according to smoking has probably decreased as well. However, given the quite high relative risks of pancreatitis associated with smoking, the fraction of cases attributable to smoking will most likely still be considerable.

Smoking may also be associated with gallstone disease (Jørgensen et al. 1990; Jørgensen 1989). If so, observed associations between smoking and pancreatitis could be explained by an increased risk of gallstones in individuals who smoke, which, in turn, renders these individuals at high risk of pancreatitis. To test this hypothesis, we performed analyses including gall stones as a time dependent variable. As expected, gallstones were strongly associated with pancreatitis risk (11, 95% CI: 7.7-15); however, including gallstones had very little influence on the relative risk of pancreatitis associated with smoking, indicating that gallstone disease does not mediate the association between smoking and pancreatitis.

In conclusion, smoking is associated with an increased risk of pancreatitis and in both men and women. The risk associated with smoking is independent of alcohol and of gallstone disease; two risk factors suggested as being the main causes of pancreatitis.
4. CONCLUSIONS

The low risk of coronary heart disease (CHD) in light to moderate alcohol drinkers was consistently observed in men and women, was independent of genetic variation in alcohol dehydrogenase genotypes ADH1B and ADH1C, and was of similar relative size in young adults, middle-aged and older individuals. However, since younger adults are at low risk of CHD, the absolute beneficial effect was small in the young. In contrast, drinking pattern had independent effects on CHD risk: a frequent intake appeared to be the most important factor for the cardioprotective effect of alcohol, whereas occasional heavy drinking was associated with increased CHD risk.

The risk of atrial fibrillation according to alcohol intake was consistent with a threshold-like relationship; for light to moderate alcohol intake there was no increase in the risk, while more heavy consumption was associated with a higher risk. This relationship did not appear to be related to the adverse effects of heavy drinking on CHD or blood pressure.

The risk of liver damage and disease was strongly associated with the amount of alcohol intake; we observed stepwise increasing signs of liver damage with increasing alcohol intake, from none through moderate and excessive intake with no apparent threshold effect. The risk of liver damage and disease was not associated with ADH1B and ADH1C genotypes.

The risk of pancreatitis was associated with alcohol in the general population, a relation that seemed independent of the alcohol drinking pattern.

Smoking was associated with the risk of developing pancreatitis and this effect was independent of alcohol intake and gallstone disease. The risk of pancreatitis was increased approximately 3-fold among smokers (as compared with never smokers), which was similar to the risk associated with heavy drinking (relative to nondrinking).

5. PERSPECTIVES

For public health purposes, the effects of alcohol on diseases and conditions should not be considered in isolation. However, the emerging and consistent evidence that the beneficial effects of alcohol are not attained by episodic binge drinking and that the risk of coronary heart disease increases among individuals with a binge-like drinking pattern is of considerable public health relevance. It remains to be tested how the risk of atrial fibrillation and pancreatitis according to alcohol depends upon the drinking pattern.

Young adults (39-50 years) seem to have the same relative benefit of a low to moderate alcohol intake according to CHD risk as middle-aged and older individuals. Caution should be taken when interpreting this finding in a public health setting, because other alcohol-related diseases and conditions in this age group were not accounted for. For public health purposes, the association between alcohol and all-cause mortality is essential because it reflects net loss of life attributable to alcohol consumption and, thus, constitutes the scientific basis for creating guidelines on sensible drinking. For even younger individuals, the risk of coronary heart disease is practically zero and beneficial effects of alcohol are thus negligible. Further, binge drinking is more prevalent among young people than among older individuals, and hazardous implications of a binge-like drinking pattern, such as an increased risk of traffic accidents and injuries, most likely predominate among the young.

Smoking is a strong risk factor for the development of pancreatitis and should be recognized as such. For instance, pancreatitis should be included in overall assessments of the harmful consequences of smoking on morbidity and mortality and of the economic consequences to society. In future work, the effect of changes of smoking behavior should be studied. Specifically, the effect of the time since quitting smoking is interesting to study when the excess risk associated with smoking declines.

Obviously, alcohol has effects on numerous other diseases and conditions, and many other factors are of importance besides those considered in this thesis. For instance, individuals with a family history of alcoholism may be better off abstaining completely from drinking alcohol. In an optimal setting, the balance between alcohol’s beneficial and harmful effects should be achieved. The most important factors in this equation may very well be to keep the amount of alcohol intake in the light to moderate range and to avoid binge drinking.

6. SUMMARY

Alcohol is used all over the world and in most Western societies, the average intake is high. Alcohol is associated with more than 60 diseases and globally, 4% of all deaths are attributable to alcohol.

The aim of the present thesis is to study associations between alcohol intake and risk of coronary heart disease (CHD), atrial fibrillation, liver cirrhosis and pancreatitis, and more specifically, to review the data for differential effects of alcohol according to modifying factors on these diseases.

The thesis is based on the results from 10 epidemiological studies, conducted in the Copenhagen City Heart Study, the Diet, Cancer and Health Study and the Pooling Project of Diet and Coronary Disease. In all study cohorts, a lower risk of CHD was observed in light and moderate alcohol drinkers. In the Copenhagen City Heart Study, we also found that increasing alcohol intake was associated with increasing HDL cholesterol and non-fasting triglycerides, higher systolic and diastolic blood pressure and decreasing fibrinogen. In contrast, ADH1B and ADH1C genotypes were not associated with risk of CHD or with any of the cardiovascular biomarkers, and there was no indication that associations between alcohol intake and CHD and between alcohol intake and biomarkers were modified by genotypes. The finding that ADH genotypes are not modifying the association between alcohol and CHD was confirmed in the Diet, Cancer and Health Study.

In the Pooling Project of Diet and Coronary Disease, we found that the association between alcohol and relative risk of CHD was similar in young adults (39-50 years), middle-aged (50-60 years) and older individuals (60+ years). However, since the incidence of CHD is low in young adults, the incidence rate difference between nondrinkers and moderate drinkers was much smaller in young adults than in older individuals, hence, for young adults, the absolute beneficial effect of alcohol is small.

Alcohol has differential effects on the risk of mortality and CHD according to drinking pattern. In the Diet, Cancer and Health Study, we found that for the same weekly amount of alcohol intake, a non-frequent intake implied a higher risk of
death than a frequent one. For CHD, drinking frequency may be the primary determinant of the inverse association between alcohol intake and CHD: The risk of CHD was lower among men who drank alcohol on more days of the week, compared to men who drank alcohol on fewer days of the week, independent of the total weekly amount of alcohol intake.

The risk of atrial fibrillation according to alcohol intake seems to be threshold-shaped; in the Copenhagen City Heart Study, no increased risk was observed among light to moderate drinkers and an increased risk only among individuals drinking >35 drinks per week.

Also in the Copenhagen City Heart Study, the risk of liver cirrhosis was strongly associated with increasing alcohol intake. Further, we found that increasing alcohol intake associated with biomarkers for liver damage (alanine aminotransferase, albumin, alkaline phosphatase, bilirubin, coagulation factors II, VII and X, γ-glutamyl transpeptidase and mean erythrocyte volume). In contrast, ADH1B and ADH1C genotypes were not associated with a risk of liver cirrhosis or with any of these biomarkers, and there was no indication that associations between alcohol intake and liver cirrhosis and between alcohol intake and biomarkers were modified by genotypes.

Finally, we observed that alcohol intake was associated with an increased risk of pancreatitis. Smoking was also associated with an increased risk of pancreatitis, which was independent of alcohol and of gallstone disease; two risk factors suggested as being the main causes of pancreatitis.

In conclusion, the results show that the association between alcohol and CHD is independent of genetic variation in alcohol-degrading enzymes. The alcohol drinking pattern is independently associated with risk of coronary heart disease and all-cause mortality. The beneficial effect of alcohol on CHD is observed among both young adults, middle-aged and elderly, but the magnitude of the absolute beneficial effect is least among the young adults. Both alcohol and smoking are associated with increased risk of pancreatitis. These results are important for future studies of the biological effects of alcohol on health and for public guidelines on alcohol.

7. **DANSK RESUMÉ**

Alkohol er forbundet med risikoen for mere end 60 sygdomme og cirka 4% af alle dødsfald kan tilskrives alkohol. Alkoholindtaget er højt i de fleste vestlige lande.

Formålet med nævneværende afhandling er at undersøge sammenhængen mellem alkoholforbrug og risiko for koronar hjertesygdom, atriefilmmere, levercirrhose og pankreatitis, og sammenhængen mellem alkohol og koronar hjertesygdom er afhængig af disse genotyper, men det var ikke tilfældet, ligesom sammenhængen mellem alkohol og kardiovaskulære biomarker heller ikke afhæng af ADH1B og ADH1C genotyperne.

Vi undersøgte sammenhængen mellem alkohol og koronar hjertesygdom blandt unge voksne (39-50 år), midldre (50-60 år) og ældre individer (60+ år). De relative risici var af samme størrelse i de tre aldersgrupper, men eftersom incidensen af koronar hjertesygdom er lav blandt unge voksne, var incidensraterne i de tre aldersgrupper med større mindre hos unge voksne end hos ældre aldersgrupper. Den absolutte gavnlige effekt af alkohol blandt unge voksne er derfor lille.

Vi sammenlignede også risikoen for at dø blandt personer med det samme ugentlige alkoholforbrug men med forskellig drukkefrekvens. Risikoen for at dø var større blandt kvinder med et ugentligt forbrug på over 7 genstande og blandt mænd med et ugentligt forbrug på over 14 genstande som indtog alkoholen på én dag sammenlignet med mænd og kvinder med det samme ugentlige forbrug spredt udover flere af ugens dage. For koronar hjertesygdom syntes drukkefrekvensen at være vigtig for den inverse sammenhæng mellem alkoholforbrug og koronar hjertesygdom: Risikoen var lavere blandt mænd, der drak alkohol på flere af ugens dage sammenlignet med mænd, der drak alkohol på færre af ugens dage. Dette fund var uafhængigt af det samlede ugentlige alkoholforbrug.

Risikoen for atriefilmmen var øget blandt personer, som drak mere end 35 genstande om ugen. For lavere alkoholforbrug var risikoen for atriefilmmere ikke øget sammenlignet med risikoen blandt allmindelige.

Risikoen for levercirrhose var stærkt forbundet med stigende alkoholforbrug. Desuden fandt vi at stigende alkoholforbrug er forbundet med biomarker for leverfikser (alaninaminotransferase, albumin, alkalisk fosfatase, bilirubin, koagulationsfaktorer II, VII og X, γ-glutamyl transpeptidase og erythrocytovolumen). Disse sammenhænge var uafhængige af ADH1B og ADH1C genotyperne.

Endelig observerede vi, at alkohol var forbundet med en øget risiko for pankreatitis. Rygning var også forbundet med en øget risiko for pankreatitis, hvilket var uafhængigt af alkohol og af galdestesssygdom, som er de to risikofaktorer, som anses for at være de væsentligste årsager til pankreatitis.

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Prospective study of alcohol drinking patterns and coronary heart disease in women and men
Janne Tolstrup, Majken K Jensen, Anne Tjønneland, Kim Overvad, Kenneth J Mukamal, Morten Grønbæk

Abstract

Objective To determine the association between alcohol drinking patterns and risk of coronary heart disease in women and men.


Participants 28 448 women and 25 052 men aged 50-65 years, who were free of cardiovascular disease at entry to the study.

Main outcome measures Incidence of coronary heart disease occurring during a median follow-up period of 5.7 years.

Results 749 and 1283 coronary heart disease events occurred among women and men. Women who drank alcohol on at least one day a week had a lower risk of coronary heart disease than women who drank alcohol on less than one day a week. Little difference was found, however, between drinking frequency: one day a week (hazard ratio 0.64, 95% confidence interval 0.51 to 0.81), 2-4 days a week (0.63, 0.52 to 0.77), five or six days a week (0.79, 0.61 to 1.03), and seven days a week (0.65, 0.51 to 0.84). For men an inverse association was found between drinking frequency and risk of coronary heart disease across the entire range of drinking frequencies. The lowest risk was observed among men who drank daily (0.50, 0.48 to 0.71) compared with men who drank alcohol on less than one day a week.

Conclusions Among women alcohol intake may be the primary determinant of the inverse association between drinking alcohol and risk of coronary heart disease whereas among men, drinking frequency, not alcohol intake, seems more important.

Introduction

Prospective studies have consistently reported a lower risk of coronary heart disease among consumers of moderate alcohol compared with abstainers. A few studies have investigated this association by also including various measures of alcohol drinking patterns. Results consistently imply that the pattern of drinking is important and that steady drinking is more beneficial than drinking in binges. In a recent such study among men it was suggested that drinking frequency is the primary determinant of the inverse association between alcohol intake and coronary heart disease, and that alcohol intake is of minor importance. Some issues still warrant consideration however; most importantly, data on the importance of drinking patterns among women are limited and results obtained among men may not apply to women for different reasons. Firstly, sex differences in alcohol pharmacokinetics have been reported, suggesting that men have more efficient first pass metabolisms than women whereas women may eliminate alcohol faster than men. Secondly, oestrogen has beneficial effects on the cardiovascular system, and studies have suggested that alcohol increases oestrogen levels.

We determined the association between alcohol drinking patterns and coronary heart disease among men and women participating in a population based cohort study consisting of middle aged Danish citizens.

Methods

From December 1993 to May 1997, 160 725 Danish men and women were invited to participate in the diet, cancer, and health study. Eligible cohort members were born in Denmark and had no previous cancers. Overall, 27 178 men and 29 875 women agreed to participate (response rate 35%). A detailed food frequency questionnaire consisting of 192 items was enclosed with the invitation. This questionnaire was checked by an interviewer during a clinic visit, when another questionnaire concerning lifestyle and background factors was completed.

In the food frequency questionnaire alcohol intake was reported as the average amount over the preceding year. Total intake was calculated and converted into number of standard drinks, defined as containing 12 g of ethanol. Drinking frequency was reported in the background questionnaire in predefined categories (never, less than once a month, 1-3 times monthly, once a week, 2-4 times weekly, 5 or 6 times weekly, and daily). We defined abstainers as those who reported no alcohol intake (amount) and no drinking occasions (frequency). To increase homogeneity among abstainers we excluded 786 people who reported no amount but a frequency greater than zero (or vice versa). We also excluded people with missing information (n = 303) or with conflicting answers on amount and frequency of alcohol intake (n = 97). In all, 53 500 people were eligible for this study.

Follow-up

We obtained information on coronary heart disease from the Danish Hospital Discharge Register and from the Danish Register of Causes of Death, where, respectively, all admissions to hospital for somatic conditions and causes of death in Denmark are registered. The hospital register is updated to 2002, whereas the causes of death register, which contains information on fatal incidents of coronary heart disease, is updated to 2000. In the period that was covered by both registers, the causes of death register contributed information on only 8% of cases. Hence we decided to end follow-up at January 2002, being aware that information on some fatal cases would be missed from January 2000 to January 2002.
In both registers diagnoses are classified according to the international classification of diseases, eighth and 10th revisions (codes for coronary heart disease: ICD-8, 410-414 and ICD-10, I20-I25). We obtained vital status of the participants from the National Central Person Register. To minimise the risk of including preclinical cases, we included 2367 participants who, at baseline, were registered with any cardiovascular disease (ischaemic stroke, arrhythmias, congestive heart failure, or peripheral artery disease).

We observed participants from enrolment until date of coronary heart event (n = 2113), death from other causes (n = 1483), emigration (n = 183), loss to follow-up (n = 3), or 1 January 2002, whichever came first.

Statistical analysis
We calculated risk estimates using Cox proportional hazard regression models, with delayed entry implemented (SAS/STAT program software). To ensure maximal adjustment for confounding by age we used age as the time axis. We adjusted the risk estimates for known risk factors for coronary heart disease: length of school education (short, ≤7 years; medium, 8-10 years; long, ≥11 years); smoking (never; former; current, 1-14, 15-24, or >24 g of tobacco/day); physical activity during leisure time (dummy variables were coded for each of the following activities: sports, walking, bicycling, housework, gardening, do it yourself); body mass index (modelled as linear splines, with knots set at 20 and 25); total intake of fruit, vegetables, and fish; and percentage of total energy intake from saturated fat (all as continuous variables). We calculated the total intake of different dietary factors using the software program Food Calc (release 1.3, www.FoodCalc.dk). Using linear splines with knots set at quintiles of the covariate in question we evaluated the assumed linearity of quantitative risk factors. We tested assumptions of the proportional hazards model but detected no violations.

To test for linear trends we treated the median value within categories continuously. We did not include abstainers when testing for trend because they may have different trait and health status than people who consume alcohol lightly to moderately, thereby biasing the results, we carried out analyses to compare the association between drinking frequency and coronary heart disease only including early cases—that is, cases that occurred within the first two years of follow-up (n = 200 women and n = 381 men)—with the association including only later cases (n = 549 women and n = 902 men). An inverse association was observed in both groups (data not shown).

Results
Overall, 53,500 people were eligible for our study: 28,448 women and 25,052 men. Women consumed a median of 5.5 alcoholic drinks a week (fifth to 95th centiles, 0.3-24) and men 11.3 (1.1-47). Drinking frequency was highly correlated with amount of alcohol intake among both women and men (r = 0.86 and r = 0.78).

Infrequent drinkers (less than one day a week) and daily drinkers (daily) were more likely to be smokers, to have a lower intake of fruit and vegetables, and to be less educated than participants in the in between drinking frequencies (table 1). Body mass index was inversely associated with drinking frequency and frequent drinkers had the lowest body mass index. These trends were the same for both sexes. Generally, fewer women than men were current and heavy smokers (>25 g of tobacco daily) and women had more hours of physical activity a week and consumed more fruit and vegetables.

During follow-up (median 5.7 years, range 0.01-8.10) 749 women and 12,835 men developed coronary heart disease. Information on 1935 of these cases came from the Danish Hospital Discharge Register. Based on incidence rates from the general population the expected number of cases from this register was 716 women (737 observed) and 1217 men (1196 observed). The observed number did not differ significantly from the expected (P > 0.10).

Amount of alcohol intake was inversely associated with coronary heart disease among women and men (figure).

Among women, drinking on at least one day a week was associated with a lower risk of coronary heart disease than drinking more rarely than one day a week (table 2). Hazard ratios were similar for drinking on one day a week (0.64, 95% confidence interval 0.51 to 0.81), 2-4 days a week (0.63, 0.52 to 0.77), five or six days a week (0.79, 0.61 to 1.03), and seven days a week (0.65, 0.51 to 0.84). A test for trend not including women that were drinking more rarely than one day a week was statistically insignificant (P = 0.49).

Among men, drinking frequency was inversely associated with risk of coronary heart disease over the whole range of drinking frequencies (table 2). Hazard ratios were 0.93 (0.75 to 1.16) for drinking on one day a week, 0.78 (0.66 to 0.94) for 2-4 days a week, 0.71 (0.57 to 0.87) for five or six days a week, and 0.59 (0.48 to 0.71) for seven days a week (P for trend < 0.0001). The test for linear trend remained statistically significant after excluding men drinking more rarely than on one day a week (P = 0.0001).

A statistically significant interaction was found between sex and drinking frequency on the risk of coronary heart disease (P = 0.02).

Table 3 lists the hazard ratios of coronary heart disease for different combinations of alcohol amount and drinking frequency. Within similar categories of drinking frequency, women drinking the largest amounts generally had the lowest risk. For example, among women drinking on 2-4 days a week the hazard ratio was 0.78 (0.63 to 0.97) for 1-6 drinks a week, 0.71 (0.57 to 0.96) for 7-13 drinks a week, and 0.27 (0.13 to 0.58) for 14 or more drinks a week (P for trend < 0.0001). For men, hazard ratios were generally lowest for the most frequent intake within similar categories of amount (table 3). For example, among men drinking on average 7-13 drinks a week, hazard ratios of coronary heart disease were 0.89 (0.62 to 1.29) for drinking alcohol on one or less days a week, 0.81 (0.67 to 0.98) for 2-4 days a week, and 0.66 (0.52 to 0.83) for 5-7 days a week (P for trend = 0.0001). Within categories of drinking frequency, hazard ratios tended to be similar.

To examine the possibility that latent baseline symptoms of coronary heart disease such as angina pectoris might reduce the frequency of drinking alcohol, thereby biasing the results, we carried out analyses to compare the association between drinking frequency and coronary heart disease only including early cases—that is, cases that occurred within the first two years of follow-up (n = 200 women and n = 381 men)—with the association including only later cases (n = 549 women and n = 902 men). An inverse association was observed in both groups (data not shown).
The frequency of drinking alcohol is inversely associated with risk of coronary heart disease among men and this was independent of alcohol intake. Among women, alcohol intake and not drinking frequency was inversely associated with coronary heart disease.

A limitation of our study is that only 35% of the invited people participated and hence caution should be taken when generalising our findings. People who choose to participate may have a different risk profile and be in better health than those who decline. However, the observed incidence of coronary heart disease did not differ from that of the general population.

We found that the association between drinking frequency and coronary heart disease was different for men and women. The number of cases was substantially lower among women than among men, however, and hence results for women are less certain and warrant further study.

We cannot exclude the possibility that participants with early symptoms of coronary heart disease at baseline had reduced their drinking frequency, explaining the inverse association. However, this association persisted when we analysed early cases separately, indicating that the observed association is unlikely to be explained by this possible bias.

Some unhealthy traits (smoking and a low intake of fruit and vegetables) were common at both extremes of drinking frequency. Everyday drinking may be associated with borderline addictive behaviour, and a strong association between smoking and...
and drinking has been observed in many studies. For the most rare drinkers, the unhealthy lifestyle may be explained by the fact that they were the poorest educated, which probably correlates with low social status. Also this category may include former alcoholics. Together, results for the extremes of drinking frequency are more likely to be residually confounded than results for the in between drinking frequencies and should be interpreted with caution. However, at least among men, we found an inverse association between drinking frequency and coronary heart disease over the entire range of drinking frequencies.

Drinking patterns in our study were constructed by combining information on average intake with drinking frequency, as done in another study. We have avoided the term “binge drinking,” which is mostly defined as drinking a minimum number of drinks per occasion and we cannot comment on this with the present data.

Several explanations may account for a possible interaction between sex and drinking frequency. One explanation is sex specific drinking habits, such as drinking with meals. We cannot exclude that men who drink frequently are more likely to drink with meals, which may contribute to a greater risk reduction with low social status. Also this category may include former alcoholics. Together, results for the extremes of drinking frequency are more likely to be residually confounded than results for the in between drinking frequencies and should be interpreted with caution. However, at least among men, we found an inverse association between drinking frequency and coronary heart disease over the entire range of drinking frequencies.

Drinking patterns in our study were constructed by combining information on average intake with drinking frequency, as done in another study. We have avoided the term “binge drinking,” which is mostly defined as drinking a minimum number of drinks per occasion and we cannot comment on this with the present data.

Several explanations may account for a possible interaction between sex and drinking frequency. One explanation is sex specific drinking habits, such as drinking with meals. We cannot exclude that men who drink frequently are more likely to drink with meals, which may contribute to a greater risk reduction compared with men with a less frequent alcohol intake. The beneficial effect of meal related alcohol intake is, however, controversial. It is unlikely that wine drinking, which may be more beneficial than drinking beer or spirits, is responsible for our results because it has been shown that wine drinkers in this cohort drink less often than beer drinkers.

Differences in alcohol pharmacokinetics between sexes may be another explanation.

The association between alcohol and coronary heart disease among women may be modified by menopausal status. Oestrogens have beneficial effects on the cardiovascular system, protecting women until menopause, when the incidence rapidly approaches that among men. Moderate alcohol drinking is thought to increase oestrogen levels. Few women in this study (17%) were premenopausal and our findings may be limited to postmenopausal women.

The inverse association between alcohol and coronary heart disease can be explained by several biologically plausible mechanisms, including dose dependent effects on high density lipoprotein levels, lower plasma fibrinogen levels, and reduced platelet aggregation. These potential beneficial effects of alcohol must be considered along with potential adverse effects of a high intake, such as high blood pressure and increased triglyceride levels. The question is if the balance between beneficial and harmful effects is affected by drinking pattern. Heavy weekend drinkers have been found to have a higher daily blood pressure and to have greater between day variability in blood pressure than heavy daily drinkers. Results are conflicting as to whether drinking pattern modifies lipid levels. Some studies found that only regular drinking can raise high density lipoprotein levels, whereas others found this among weekend drinkers. The presumed lowering effect of alcohol on fibrinogen levels has been found to be independent of drinking pattern (daily versus weekend drinking).

It has not been investigated if drinking pattern affects the presumed association between alcohol and increased oestrogen levels among women.

Table 2 Hazard ratios (95% confidence intervals) of coronary heart disease according to drinking frequency among women and men

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency of drinking alcohol (days/week)</th>
<th>P for trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of cases</td>
<td>24</td>
<td>276</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>1.01 (0.66 to 1.53)</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted for multiple factors†</td>
<td>0.92 (0.61 to 1.41)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

| Men:     |                                          |             |
| No of cases | 39 | 180 | 140 | 424 | 195 | 305 |         |
| Adjusted for age | 1.38 (0.98 to 1.95) | 1.00 | 0.86 (0.69 to 1.07) | 0.69 (0.58 to 0.83) | 0.65 (0.53 to 0.79) | 0.60 (0.50 to 0.73) | <0.0001 |
| Adjusted for multiple factors† | 1.44 (1.02 to 2.04) | 1.00 | 0.93 (0.75 to 1.16) | 0.78 (0.66 to 0.94) | 0.71 (0.57 to 0.87) | 0.59 (0.48 to 0.71) | <0.0001 |

*Never drinkers not included in analyses for trend.
†Age, smoking, education, physical activity, body mass index, total intake of fruit, vegetables, fish, and saturated fat.
‡P for trend was 0.49 when women were excluded who never drink or drink on less than one day a week.

Table 3 Hazard ratios (95% confidence intervals) of coronary heart disease according to drinking frequency and amount of alcohol intake among women and men

<table>
<thead>
<tr>
<th>Alcohol intake (drinks/week)</th>
<th>Frequency of drinking alcohol (days/week)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.03 (0.68 to 1.56) (n=24)</td>
<td></td>
</tr>
<tr>
<td>1-6</td>
<td>1.00 (n=960)</td>
<td></td>
</tr>
<tr>
<td>7-13</td>
<td>0.87 (0.53 to 1.41) (n=9)</td>
<td>0.57</td>
</tr>
<tr>
<td>≥14</td>
<td>0.65 (0.18 to 2.61) (n=2)</td>
<td>0.01</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.47 (1.05 to 2.08) (n=29)</td>
<td></td>
</tr>
<tr>
<td>1-6</td>
<td>1.00 (n=278)</td>
<td>0.02</td>
</tr>
<tr>
<td>7-13</td>
<td>0.89 (0.62 to 1.29) (n=31)</td>
<td>0.0001</td>
</tr>
<tr>
<td>≥21</td>
<td>1.00 (0.32 to 3.13) (n=3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.25</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Hazard ratios are adjusted for age, education, smoking, physical activity, body mass index, and total intake of vegetables, fruit, fish, and saturated fat. Number of cases in parentheses.
Heavy alcohol drinking is positively associated with many problems such as liver diseases, cancers, and road crashes, and overall mortality is higher among individuals with a high alcohol intake compared with light consumers, reflecting that the beneficial effects of alcohol on coronary heart disease is by far exceeded by the detrimental effects of alcohol at these levels. Also, the beneficial effect of alcohol is probably confined to middle aged or older people. Therefore the inverse association between alcohol intake and coronary heart disease should be viewed in this context when giving public health advice. In conclusion, we found that drinking frequency seemed to be the main determinant of the inverse association between alcohol intake and coronary heart disease among men, which confirms results from another study. For women, amount of alcohol may be more important than frequency.

We thank the participants of the diet, cancer, and health study.

Contributors: JT contributed to the conception and design of the study, the analysis and interpretation of data, and wrote the manuscript. MKJ, KJM, and MG contributed to the conception and design of the study, interpretation of data, and to critically revising the paper. AT and KO contributed to the design of the study, the acquisition of data, interpretation of data, and critically revising the paper. All authors approved the final version of the article. Katja Boll prepared the data file and Søren Rasmussen calculated incidence rates of coronary heart disease in the general Danish population. MG is the guarantor.

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Ethical approval: This study was approved by the ethical committees for the Copenhagen and Aarhus municipalities (KF 01-116/96).

Alcohol Intake, Myocardial Infarction, Biochemical Risk Factors, and Alcohol Dehydrogenase Genotypes

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http://circgenetics.ahajournals.org/cgi/content/full/2/5/507
**Alcohol Intake, Myocardial Infarction, Biochemical Risk Factors, and Alcohol Dehydrogenase Genotypes**

Janne S. Tolstrup, MS, PhD; Morten Grønbæk, MD, DrMedSci; Børge G. Nordestgaard, MD, DrMedSci

**Background**—The risk of myocardial infarction is lower among light-to-moderate alcohol drinkers compared with abstainers. We tested associations between alcohol intake and risk of myocardial infarction and risk factors and whether these associations are modified by variations in alcohol dehydrogenases.

**Methods and Results**—We used information on 9584 men and women from the Danish general population in the Copenhagen City Heart Study. During follow-up, from 1991 to 2007, 663 incident cases of myocardial infarction occurred. We observed that increasing alcohol intake was associated with decreasing risk of myocardial infarction, decreasing low-density lipoprotein cholesterol and fibrinogen, increasing diastolic and systolic blood pressure and high-density lipoprotein cholesterol, and with U-shaped nonfasting triglycerides. In contrast, ADH1B and ADH1C genotypes were not associated with risk of myocardial infarction or with any of the cardiovascular biochemical risk factors, and there was no indication that associations between alcohol intake and myocardial infarction and between alcohol intake and risk factors were modified by genotypes.

**Conclusions**—Increasing alcohol intake is associated with decreasing risk of myocardial infarction, decreasing low-density lipoprotein cholesterol and fibrinogen, increasing diastolic and systolic blood pressure and high-density lipoprotein cholesterol, and U-shaped nonfasting triglycerides. These associations were not modified by ADH1B and ADH1C genotypes. *(Circ Cardiovasc Genet. 2009;2:507-514.)*

**Key Words:** blood pressure ■ genetics ■ cardiovascular diseases ■ myocardial infarction ■ epidemiology ■ alcohol ■ cardiovascular risk factors ■ alcohol dehydrogenase genes

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Substantial epidemiological evidence suggests that alcohol has beneficial effects on the cardiovascular system.1–3 First, a lower risk of coronary heart disease among light-to-moderate alcohol consumers compared with abstainers is consistently observed in different populations.6 Second, plausible mediating factors such as increased high-density lipoprotein (HDL) cholesterol levels and reduced low-density lipoprotein (LDL) cholesterol and plasma fibrinogen levels have also been identified.7,8 In recent research, focus has been on identifying possible genetic and environmental modifiers of the association between alcohol and coronary heart disease. Specifically, it has been suggested that the effect of alcohol on the risk of coronary heart disease depends on variations in genes coding for alcohol-degrading enzymes: individuals carrying genotypes that code for slow alcohol degradation has persistently higher blood alcohol concentrations that leads to a lower risk of coronary heart disease compared with individuals with genotypes that code for fast alcohol degradation.

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**Clinical Perspective on p 514**

Alcohol degradation is mainly catalyzed by different alcohol dehydrogenases (ADHs). In vitro studies have shown that at ADH1B, alleles ADH1B·2 and ADH1B·1 produce enzymes with a 38-fold difference in alcohol degradation rate, and at ADH1C, alleles ADH1C·1 and ADH1C·2 produce enzymes with a 2.5-fold difference.9 However, the size of in vivo effects of these variations is much more modest and not even consistently observable.10–15 In whites, the frequency of the most active alleles (ADH1B·2 and ADH1C·1) are ≈2% and 58%.16

Although the idea that the risk reduction of coronary heart disease in low-to-moderate drinkers depends on the genetic capacity for alcohol degradation is both appealing and plausible, the evidence for this modification is sparse and inconsistent. In the first study on the subject, which was conducted among American physicians, ADH1C slow metabolizers seemingly had a lower risk of myocardial infarction (MI) than ADH1C fast metabolizers, but this was confined to individuals in the highest drinking category17; however, this is in contrast to findings from another study, where this effect was only observed in men with a very low intake (less than 3 drinks per week).18 In some other studies, no significant interaction between the ADH1C genotype and alcohol on risk of coronary heart disease was found.19–21 The potential
interaction between ADH1B genotypes and alcohol has not been addressed among whites, most likely because the ADH1B·2 allele is relatively rare in this population.

In this study, we aim at testing the association between alcohol intake and risk of MI, and whether this association is modified by ADH1B and ADH1C genotypes. We also tested the association between alcohol intake and cardiovascular biochemical risk factors, such as blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, and fibrinogen, and whether these associations differ according to genotype.

Methods

Study Population
Our data originates from the Copenhagen City Heart Study, which is a series of studies conducted in the Danish general population. Examinations consisted of interview, physical examination, and, more especially, blood was given for DNA purification at the examination that was performed in 1991–1994. Enrollment and examination procedures have been described in more detail elsewhere. All participants gave informed consent, and the ethics committee for Copenhagen and Frederiksberg approved the study (100.2039/91).

Questionnaire Measures
Amount of usual alcohol intake was reported as weekly consumption of beer (in bottles), wine (in glasses), and spirits (in units). Assuming 1 drink to be equal to 12 g of pure alcohol, a measure of total weekly alcohol intake was calculated. Smoking was reported as status (never, former, or current) and amount of smoking (in number of daily cigarettes, cheroots, cigars, and pipes). Assuming 1 cigarette to be equivalent to 1 g of tobacco, 1 cheroot or 1 cigar to be equivalent to 3 g of tobacco, and 1 pipe to be equivalent to 5 g of tobacco, total amount of daily smoking was calculated. School education was reported as number of years of basic schooling and categorized as <8, 8 to 11, and >11 years of education, corresponding to lower primary school, higher primary school, and secondary school. Participants were classified as having diabetes, hypertension, or hypercholesterolemia if they reported a physician-made diagnosis. Familial predisposition to cardiovascular disease was defined as having 1 or 2 affected parents before the age 60 years. Among women, we used information on menstruations and hormone replacement therapy to define their menopausal status in categories of pre and post-menopausal with and without hormone replacement therapy.

Clinical and Laboratory Measures
Arterial blood pressure was measured in the left arm with the participant in the sitting position after 5 minutes of rest. Study staff obtained blood samples and measured height and weight. Total plasma cholesterol, plasma HDL cholesterol, plasma nonfasting triglycerides, and plasma fibrinogen were measured using standard hospital assays (Boehringer Mannheim) subjected to daily internal quality control assessing assay precision and monthly external quality control assessing assay accuracy. The ADH1B·2 allele (rs1229984, Arg47His in exon 3) and ADH1C·2 allele (rs698, Ile349Val in exon 8) were identified by means of duplex polymerase chain reaction followed by Nanogen microelectronic chip technology (Nanogen NMW 1000 Nanochip Molecular Biology Workstation) using standard conditions (details available from authors). In a validation study, the accuracy of the Nanogen method was found to be comparable with restriction fragment length polymorphism.

Assessment of MI and Vital Status
Information on MI was obtained from the Danish Patient Registry and the Danish Causes of Death Registry, where. Registration System, where information on address and vital status are registered for every Danish citizen.

Statistical Analysis
Of the 17 180 individuals who were invited to the 1991–1994 examination, 10 135 participated (59%). Participants of Asian or black descent (n = 161), missing questionnaire data (n = 74), and acute MI before baseline (316) were excluded, leaving 9584 individuals. Of these, 8777 had given blood and 8740 were successfully genotyped for ADH1B and ADH1C. In all analyses, ADH1B·1/2 was combined with ADH1B·2/2 because of the low number in the latter group (n = 5).

We used the χ² test to determine whether the ADH1B and ADH1C genotypes were in Hardy-Weinberg equilibrium. Haplotype frequencies for calculation of linkage disequilibrium coefficients were estimated by HPlus. Linkage disequilibrium coefficients Lewontin’s D’ = 0.90 and the correlation coefficient r² was 0.01 between ADH1B·2 and ADH1C·1, both coding for the fast alcohol degradation enzymatic forms.

Risk estimates for acute MI during follow-up were computed by means of Cox proportional hazard regression models. Age was used as the time axis to ensure that the estimation procedure was based on comparisons of individuals at the same age and hence remove confounding by age. The observation time for each participant was the period from the Copenhagen City Heart Study 1991–1994 examination, until date of MI, death from other causes, emigration outside Denmark, or August 1, 2007, whichever came first. We had follow-up information on all participants.

Test for linear trend was performed by treating the median within alcohol categories as a continuous variable and tests for interaction between genotypes and alcohol were performed by comparing a model including main effects of alcohol and ADH1C genotypes with a model also including the interaction terms by a log likelihood test. Associations between alcohol intake, ADH1B and ADH1C genotypes and blood pressure, HDL, LDL, triglyceride, and fibrinogen were investigated by general linear models (all log-transformed to approximate normal distributions). Tests for effects of a low-to-moderate alcohol intake (<14 drinks/week for women and <21 drinks/week for men) on blood pressure, HDL, LDL, triglyceride, and fibrinogen levels were performed by modeling alcohol intake with linear splines with a knot placed at 14 and 21 drinks per week for women and men, respectively, and testing for statistical significance for each portion of alcohol intake. Furthermore, statistically significant U-shaped effects for triglycerides were tested by including the alcohol intake as a linear and a squared term. P values less than 0.05 were considered statistically significant.

Finally, we calculated posthoc power using the Quanto program, by assuming effect sizes for the ADH1C-alcohol interaction as in the study by Hines et al., and by using information on distribution on alcohol intake and genotype and number of MI cases from our study. Assuming a significance level of 0.05, we had 97% power to pick up an ADH1C-alcohol interaction of a size similar to what was found in the Hines study.
Results

Baseline Characteristics

Of the 9584 participants, 4105 (57%) were women, and the median age of participants was 61 years (10–90%, 35 to 77). The median alcohol intake was 3.0 drinks/wk among women and 10 drinks/wk among men (Table 1). Approximately half of the participants were current smokers. Frequencies of ADH1B · 1/2/2/2 and of ADH1C · 1/1 (genotypes coding for the most active enzymes) were 4.5% and 34%, ADH1B and the ADH1C genotypes were both in Hardy-Weinberg equilibrium ($P = 0.43$ and 0.64, respectively).

Alcohol Intake/ADH1B/ADH1C/Genotypes, and Risk of MI

Increasing amount of alcohol intake was associated with decreasing risk of MI among men and women (Figure 1). In contrast, ADH1B and ADH1C genotypes were not associated with risk of MI in men or women (Table 2).

The association between alcohol intake and risk of MI was not modified by ADH1C genotype, because hazard ratios were comparable within strata of ADH1C genotype (Figure 2); the probability value for interaction between ADH1C genotype and alcohol intake was 0.56 in a model combining men and women. Similar results were obtained when analyzing each sex separately. We did not have sufficient statistical power to perform similar analysis for the ADH1B genotype because the ADH1B · 2 allele is relatively rare.

Alcohol Intake/ADH1B/ADH1C/Genotypes, and Cardiovascular Biochemical Risk Factors

Among women, alcohol was statistically significantly associated with increasing levels of diastolic and systolic blood pressure and HDL cholesterol, and with decreasing levels of LDL cholesterol and fibrinogen with no apparent threshold effect (Figure 3). Also among men, alcohol was associated with decreasing levels of LDL cholesterol, but again, only for alcohol intake of 21 or more drinks/wk. There appeared to be a U-shaped association between alcohol intake and nonfasting triglycerides.

Table 1. Baseline Characteristics of 5479 Women and 4105 Men Who Participated in the Copenhagen City Heart Study 1991–1994 Examination*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral and demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62 (36, 76)</td>
<td>60 (35, 76)</td>
</tr>
<tr>
<td>Alcohol intake, drinks/wk†</td>
<td>3.0 (0, 15)</td>
<td>10 (0, 33)</td>
</tr>
<tr>
<td>School education ≤7 y, %</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>41</td>
<td>47</td>
</tr>
<tr>
<td>Amount of smoking, g/d‡</td>
<td>15 (5, 20)</td>
<td>20 (7, 30)</td>
</tr>
<tr>
<td>Low exercise intensity, %</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Postmenopausal, %</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Use of hormone replacement therapy, %</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Clinical and physiological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.4 (20.1, 31.4)</td>
<td>25.7 (21.6, 31.2)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>2.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>12.5</td>
<td>9.9</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>10.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADH1B · 1/2/2/2 (fast), %</td>
<td>4.3</td>
<td>4.6</td>
</tr>
<tr>
<td>ADH1B · 1/1 (slow), %</td>
<td>95.7</td>
<td>95.4</td>
</tr>
<tr>
<td>ADH1C · 1/1 (fast), %</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>ADH1C · 2/1 (intermediate), %</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>ADH1C · 2/2 (slow), %</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Plasma total cholesterol, mmol/L§</td>
<td>4.7 (6.2, 8.1)</td>
<td>4.5 (5.9, 7.5)</td>
</tr>
</tbody>
</table>

*Continuous characteristics are shown as median (10th, 90th percentile). †One drink corresponds to 12 g of pure alcohol. ‡Median (10th, 90th percentile), among current smokers only. §Nonfasting.

Figure 1. Hazard ratio of MI according to weekly alcohol intake. The analyses were adjusted for school education, smoking, physical activity, body mass index, diabetes, hypertension, and hypercholesterolemia. Analyses among women also adjusted for postmenopausal status and use of hormone replacement therapy. Vertical bars indicate 95% CIs for the comparison with participants who drank <1 drink per week.
ides, but it was not statistically significant ($P=0.23$). Alcohol was statistically significantly associated with increasing levels of HDL cholesterol and with decreasing levels of fibrinogen with no apparent threshold effect among men.

**ADH1B** and **ADH1C** genotypes were not consistently associated with any of these cardiovascular risk factors among women or men (Table 3). There was no sign of interaction between **ADH1C** and alcohol intake on any of the cardiovascular biochemical risk factors (all $P$ values $>0.05$).

### Discussion

In this general population study, we found that increasing alcohol intake was associated with a lower risk of MI and that amount of weekly alcohol from none to low through moderate and excessive intake was associated with stepwise increasing levels of diastolic and systolic blood pressure and HDL cholesterol, with stepwise decreasing levels of LDL cholesterol and fibrinogen, and with a U-shaped curve for nonfasting triglycerides. In contrast, **ADH1B** and **ADH1C** genotypes were not associated with risk of MI or with cardiovascular risk factors, and there was no indication that associations between alcohol intake and MI or alcohol intake and cardiovascular risk factors were modified by genotype.

A moderate alcohol intake is consistently shown to be associated with a decrease in risk of coronary heart disease. The maximal benefit seem to be obtained at 1 to 2 drinks per day for women and 2 to 3 drinks per day for men; for higher amounts of alcohol intake, there seem to be no further gain and some studies have even reported an increase in risk, indicating a J-shaped association between alcohol intake and coronary heart disease. The beneficial effect of alcohol is primarily thought to be mediated through an increase in HDL and a decrease in fibrinogen. For these 2 cardiovascular risk factors, we observed that increasing alcohol intake was associated with increasing HDL and decreasing fibrinogen.

![Figure 2. Hazard ratio of MI according to **ADH1C** genotype and weekly alcohol intake in men and women combined. The analyses were adjusted for sex, **ADH1B** genotype, school education, smoking, physical activity, body mass index, diabetes, hypertension, hypercholesterolemia, postmenopausal status, and use of hormone replacement therapy. Vertical bars indicate 95% CIs for the comparison with participants with the **ADH1C·1/1** genotype who drank <1 drink per week. The probability value was 0.56 for interaction between **ADH1C·1/1** and alcohol intake (estimated in nested log-likelihood test).](downloaded_from_circgenetics.ahajournals.org_by_on_October_21_2009)
These findings are consistent with the above mentioned effects of alcohol intake in the low-to-moderate range on the risk of coronary heart disease. We also observed that alcohol intake at higher levels (>14/21 drinks/wk for women/men) was associated with higher diastolic and systolic blood pressure and with increased level of nonfasting triglycerides, which on the other hand is associated with increased cardiovascular risk and in support of a J-shaped association between alcohol intake and risk of coronary heart disease.

If the effect of alcohol on coronary heart disease is modified by variations in genes it really comes down to the question of whether the risk is lower among (slow metabolizers) than among (fast metabolizers) among light-to-moderate drinkers but similar among nondrinkers. Initially, results in American physicians by Hines et al indicated that this is so (interaction, P = 0.01; Table 4). However, the relative risk of 0.14 (95% CI, 0.04 to 0.45) was based on only 5 cases and 37 controls with the genotype (slow metabolizers) in the highest alcohol category drinking (≥8 drinks/wk); for lower alcohol intake there seemed to be no difference in risk of MI according to genotype. Another study also found a significant interaction (P = 0.02) between alcohol intake and the genotype, but only after performing post hoc regrouping of the alcohol categories, and in contrast to the previous report, the lower risk was found among individuals with the lowest alcohol intake (0.7 to 2 drinks/wk). Finally, our study which is the largest so far could not confirm either of the previous findings; our post hoc power calculations showed that we had 97% power to pick up a alcohol-genotype interaction of a size similar to what was found in the Hines study. This further supports the overall conclusion that the association between alcohol intake and risk of coronary heart disease is not modulated by the genotype.

Previously, we showed that genotypes were associated with amount of alcohol intake and with risk of heavy drinking (participants with genotypes coding for slow alcohol degradation were drinking more and had higher risk of heavy drinking; for , however, these effects were only modest). Hence, individuals with genotypes coding for slow alcohol degradation have higher blood alcohol concentrations due to both the lower activity of the resulting enzyme and to a higher alcohol intake. These effects both stem directly from the genotype and should therefore not be separated.
A limitation of our results is that never-drinkers could not be separated from ex-drinkers and the nondrinking category may therefore contain some former alcoholics who due to their former heavy drinking have preexisting illness. This could lead to an apparent inverse association between alcohol intake and MI. However, analyses of alcohol intake and cardiovascular biochemical risk factors (diastolic and systolic blood pressure, HDL and LDL cholesterol, nonfasting triglycerides, and fibrinogen) showed that the level of the respective risk factor in the nondrinking category were in accordance with an overall dose-response shaped curved between alcohol intake and the cardiovascular risk factor, indicating that accumulation of former heavy drinkers in this category is not a major problem.

Limitations further include that information on alcohol intake was obtained by self-report and has not been validated.

<table>
<thead>
<tr>
<th>Relative enzyme activity</th>
<th>1/1</th>
<th>1/2</th>
<th>2/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>-0.06 (0.94)</td>
<td>0.31 (0.40)</td>
<td>1.08 (0.03)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>2.48 (0.05)</td>
<td>0.72 (0.20)</td>
<td>1.96 (0.01)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>-0.07 (0.30)</td>
<td>0.01 (0.57)</td>
<td>-0.01 (0.67)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.02 (0.58)</td>
<td>0.01 (0.84)</td>
<td>0.01 (0.92)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>-0.05 (0.27)</td>
<td>-0.01 (0.58)</td>
<td>-0.01 (0.76)</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>0.01 (0.94)</td>
<td>0.01 (0.93)</td>
<td>0.00 (0.99)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>1.23 (0.18)</td>
<td>0.31 (0.46)</td>
<td>-0.50 (0.35)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>2.82 (0.04)</td>
<td>0.72 (0.25)</td>
<td>0.37 (0.65)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>0.10 (0.22)</td>
<td>0.03 (0.33)</td>
<td>0.04 (0.34)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.04 (0.28)</td>
<td>0.00 (0.95)</td>
<td>-0.01 (0.50)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>-0.11 (0.10)</td>
<td>0.07 (0.05)</td>
<td>0.07 (0.11)</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>0.05 (0.28)</td>
<td>0.00 (0.96)</td>
<td>-0.03 (0.47)</td>
</tr>
</tbody>
</table>

*Numbers represent estimated differences between the ADH1B·1/1 and ADH1B·1/2; 2/2, and ADH1C·1/2 and ADH1C·1/1, and ADH1C·2/2 and ADH1C·1/1, respectively. Numbers in parentheses represent P values.

A limitation of our results is that never-drinkers could not be separated from ex-drinkers and the nondrinking category may therefore contain some former alcoholics who due to their former heavy drinking have preexisting illness. This could lead to an apparent inverse association between alcohol intake and MI. However, analyses of alcohol intake and cardiovascular biochemical risk factors (diastolic and systolic blood pressure, HDL and LDL cholesterol, nonfasting triglycerides, and fibrinogen) showed that the level of the respective risk factor in the nondrinking category were in accordance with an overall dose-response shaped curved between alcohol intake and the cardiovascular risk factor, indicating that accumulation of former heavy drinkers in this category is not a major problem.

Limitations further include that information on alcohol intake was obtained by self-report and has not been validated.

### Table 4. Summary Findings from Studies of ADH1C Genotype and Associations With Coronary Heart Disease*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Categorization of Alcohol, Drinks/wk</th>
<th>No. of Events</th>
<th>1/1</th>
<th>1/2</th>
<th>2/2</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolstrup et al†</td>
<td>&lt;1</td>
<td>175</td>
<td>1</td>
<td>1.38 (0.97 to 1.96)</td>
<td>1.60 (1.04 to 2.47)</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>1 to 13</td>
<td>307</td>
<td>0.99 (0.70 to 1.40)</td>
<td>0.98 (0.71 to 1.37)</td>
<td>0.83 (0.55 to 1.25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥14</td>
<td>146</td>
<td>0.80 (0.53 to 1.23)</td>
<td>0.82 (0.56 to 1.19)</td>
<td>0.88 (0.55 to 1.42)</td>
<td></td>
</tr>
<tr>
<td>Heidrich et al20</td>
<td>≤1</td>
<td>24</td>
<td>1</td>
<td>0.69 (0.31 to 1.55)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 to 8</td>
<td>13</td>
<td>0.56 (0.19 to 1.61)</td>
<td>0.83 (0.34 to 2.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥8</td>
<td>35</td>
<td>1.06 (0.50 to 2.25)</td>
<td>0.36 (0.16 to 0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younis et al‡18</td>
<td>&lt;1</td>
<td>44</td>
<td>1</td>
<td>0.82 (0.47 to 1.45)</td>
<td>0.64 (0.24 to 1.68)</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>1 to 5</td>
<td>64</td>
<td>0.70 (0.40 to 1.22)</td>
<td>0.56 (0.32 to 0.99)</td>
<td>0.66 (0.31 to 1.38)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥5</td>
<td>102</td>
<td>0.57 (0.33 to 0.98)</td>
<td>0.77 (0.47 to 1.26)</td>
<td>0.68 (0.36 to 1.27)</td>
<td></td>
</tr>
<tr>
<td>Djoussé et al19</td>
<td>0</td>
<td>56</td>
<td>1</td>
<td>0.67 (0.34 to 1.31)</td>
<td>1.11 (0.50 to 2.48)</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>&gt;0</td>
<td>76</td>
<td>0.74 (0.41 to 1.32)</td>
<td>0.60 (0.34 to 1.08)</td>
<td>0.53 (0.24 to 1.18)</td>
<td></td>
</tr>
<tr>
<td>Hines et al17</td>
<td>&lt;1</td>
<td>117</td>
<td>1</td>
<td>1.01 (0.58 to 1.75)</td>
<td>0.59 (0.28 to 1.23)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>1 to 8</td>
<td>191</td>
<td>1.11 (0.67 to 1.84)</td>
<td>0.66 (0.40 to 1.08)</td>
<td>1.02 (0.55 to 1.88)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥8</td>
<td>87</td>
<td>0.62 (0.34 to 1.13)</td>
<td>0.68 (0.40 to 1.15)</td>
<td>0.14 (0.04 to 0.45)</td>
<td></td>
</tr>
</tbody>
</table>

*Presented numbers are measures of relative risk (95% CIs) compared with ADH1C·1/1 nondrinkers.
†Results from the present article.
‡P for alcohol: ADH1C interaction was 0.02 after post hoc regrouping alcohol into 1 to 2 and ≥2 drinks/week (the latter risk estimates are not shown in the table).
However, associations between increasing alcohol intake and increasing levels of biomarkers of alcohol intake such as alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transpeptidase has previously been observed within this cohort. Also, because we studied nonfasting triglycerides. These associations were not modified by cholesterol and fibrinogen, increasing diastolic and systolic associated with decreasing risk of MI, decreasing LDL or genotype.

Our study had several strengths. First of all, sample size is large and the wide range of alcohol intake provided statistical power to study effects of low-to-moderate as well as excessive alcohol consumption on levels of cardiovascular risk factors and risk of MI. Furthermore, participants were men and women all from the general population of Danish descent. Hence, population stratification is unlikely to have affected our results. We had information on several different cardiovascular risk factors, which were obtained objectively from the study participants. Hence, it is unlikely that these measures are differentially biased according to alcohol intake or genotype.

In summary, we observed that increasing alcohol intake associated with decreasing risk of MI, decreasing LDL cholesterol and fibrinogen, increasing diastolic and systolic blood pressure and HDL cholesterol, and with U-shaped nonfasting triglycerides. These associations were not modified by ADH1B and ADH1C genotypes.

Acknowledgments

We thank to the participants in the Copenhagen City Heart Study for their outstanding cooperation.

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Disclosures

None.

References

CLINICAL PERSPECTIVE

Alcohol intake in moderation is associated with a lower risk of myocardial infarction. It has been suggested that this cardioprotective effect of alcohol depends on alcohol’s effect on other cardiovascular risk factors and possibly on the individual’s genetic capacity for degrading alcohol. In this large population-based study, we found that alcohol intake was associated with levels of the cardiovascular risk factors low-density lipoprotein and high-density lipoprotein cholesterol, fibrinogen, blood pressure, and nonfasting triglycerides. However, the associations between alcohol intake and risk of myocardial infarction and between alcohol intake and cardiovascular risk factors were not modified by genetic variation in alcohol dehydrogenases. Our results suggest that the protective effect of alcohol on the development of myocardial infarction does not depend on genetic variations affecting enzymes involved in alcohol metabolism.

33. QUANTO 1.1: A computer program for power and sample size calculations for genetic-epidemiology studies. 2007.

Alcohol intake in moderation is associated with a lower risk of myocardial infarction. It has been suggested that this cardioprotective effect of alcohol depends on alcohol’s effect on other cardiovascular risk factors and possibly on the individual’s genetic capacity for degrading alcohol. In this large population-based study, we found that alcohol intake was associated with levels of the cardiovascular risk factors low-density lipoprotein and high-density lipoprotein cholesterol, fibrinogen, blood pressure, and nonfasting triglycerides. However, the associations between alcohol intake and risk of myocardial infarction and between alcohol intake and cardiovascular risk factors were not modified by genetic variation in alcohol dehydrogenases. Our results suggest that the protective effect of alcohol on the development of myocardial infarction does not depend on genetic variations affecting enzymes involved in alcohol metabolism.
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Alcohol Intake and Risk of Coronary Heart Disease in Younger, Middle-Aged, and Older Adults

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Background—Light to moderate alcohol consumption is associated with a reduced risk of coronary heart disease. This protective effect of alcohol, however, may be confined to middle-aged or older individuals. Coronary heart disease incidence is low in men <40 years of age and in women <50 years of age; for this reason, study cohorts rarely have the power to investigate the effects of alcohol on coronary heart disease risk in younger adults. This study examined whether the beneficial effect of alcohol on coronary heart disease depends on age.

Methods and Results—In this pooled analysis of 8 prospective studies from North America and Europe including 192 067 women and 74 919 men free of cardiovascular diseases, diabetes, and cancers at baseline, average daily alcohol intake was assessed at baseline with a food frequency or diet history questionnaire. An inverse association between alcohol and risk of coronary heart disease was observed in all age groups; hazard ratios among moderately drinking men (5.0 to 29.9 g/d) 39 to 50, 50 to 59, and ≥60 years of age were 0.58 (95% confidence interval [CI], 0.36 to 0.93), 0.72 (95% CI, 0.60 to 0.86), and 0.85 (95% CI, 0.75 to 0.97) compared with abstainers. However, the analyses indicated a smaller incidence rate difference between abstainers and moderate consumers in younger individuals (incidence rate difference, 45 per 100 000; 90% CI, 8 to 84) than in middle-aged (incidence rate difference, 64 per 100 000; 90% CI, 24 to 102) and older (incidence rate difference, 89 per 100 000; 90% CI, 44 to 140) adults. Similar results were observed in women.

Conclusion—Alcohol is also associated with a decreased risk of coronary heart disease in younger adults; however, the absolute risk was small compared with middle-aged and older adults. (Circulation. 2010;121:1589-1597.)

Key Words: age groups ▪ alcohol consumption ▪ coronary disease ▪ epidemiology

The association between alcohol intake and coronary heart disease (CHD) has been thoroughly investigated over the past decades with regard to both the amount and type consumed. In recent years, the importance of drinking pattern has also been considered. In general, alcohol intake is consistently linked with a lower risk of CHD. Age-specific incidence rates of CHD vary considerably, being very low in men <40 years of age and in women <50 years of age. For this reason, the statistical power to investigate the effects of alcohol on CHD in younger adults is limited. Most results are obtained from cohorts consisting of middle-aged and older adults, and only a few studies have addressed the effects of alcohol on CHD in younger adults. In principle, the cause of CHD among younger adults may differ from that among older individuals; for instance, relatively more cases of CHD among younger adults may differ from that among older individuals; for instance, relatively more cases of CHD among younger adults may be attributable to genetic causes. Hence, alcohol may not necessarily protect against CHD in this age group. We pooled data from 8 studies to increase sample size and to enable the investi-
igation of associations between alcohol intake and CHD in subsets of populations defined by age group.

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Methods

Study Population

The analyses were based on data from the Pooling Project of Diet and Coronary Disease. The inclusion criteria were the following: a prospective study with at least 150 incident coronary cases, assessment of usual dietary intake, and a validation study of the diet assessment method. The following 12 studies met these criteria and agreed to share data: Adventists Health Study (AHS), Atherosclerosis Risk in Communities Study (ARIC), α-Tocopherol, β-Carotene Cancer Prevention Study (ATBC), Finnish Mobile Clinic Health Examination (FMC), Health Professionals Follow-Up Study (HPFS), Israeli Ischemic Heart Disease Study (IIHD), Iowa Women’s Health Study (IWHS), Nurses’ Health Study (NHS), Va¨sterbotten Intervention Program (VIP), and Women’s Health Study (WHS). The AHS included only nondrinkers, and the FMC and IIHD studies were excluded from the present analysis because of missing information on alcohol intake. In addition, IWHS was excluded from main analyses because of self-reported information on CHD. The 8 remaining studies are presented in Table 1. The NHS was divided into 2 segments, thereby taking advantage of repeated assessments on dietary intake and the long follow-up period. The 2 segments are referred to as NHSa (1980 to 1986) and NHSb (1986 to 1996). The second segment comprised only women who remained free of CHD after the first follow-up period, and cases were included in whichever segment they occurred.

Measurements

Average daily alcohol intake was assessed at baseline with a food frequency or diet history questionnaire inquiring about typical intake of alcoholic beverages. For each beverage, grams of daily alcohol intake were calculated from information on the amount and frequency of consumption and the alcohol content of the beverage. Study-specific conversion factors for the alcohol content were used. A standard drink contains 0.5 to 1.5 g pure alcohol. Total alcohol intake was given by the sum of the beverage-specific intakes.

The outcome of interest was incident CHD events (both fatal and nonfatal). All 8 included studies used validated methods to define nonfatal and fatal CHD cases.

Statistical Methods

Participants were excluded if they reported energy intakes beyond 3 SD from the study-specific, log-transformed mean energy intake of the baseline population (1% of the study population). Persons 35 years of age or with a history of cardiovascular disease, diabetes, or cancers (other than nonmelanoma skin cancer) were also excluded. Participants were followed up from baseline to date of CHD event, date of death, or end of follow-up, whichever occurred first. Follow-up periods <10 years (ARIC and GPS) were truncated to reduce heterogeneity. Individual studies were combined through the use of an aggregated pooled analysis technique allowing for calculation of a single exposure-effect estimate while adjusting for study origin.

The hazard ratios of CHD were ascertained by the Cox proportional-hazards regression model with age as underlying time

Table 1. Baseline Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study and Sex</th>
<th>Baseline Cohort*</th>
<th>Year of Questionnaire</th>
<th>Mean Age (90% Limit), y</th>
<th>Follow-Up, Person-y</th>
<th>CHD Cases, n</th>
<th>Alcohol Intake</th>
<th>CHD Deaths</th>
<th>Total CHD Events</th>
<th>Median (5th–95th Percentile), g/d</th>
<th>Abstainers, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC</td>
<td>Male</td>
<td>5217</td>
<td>1987–1989</td>
<td>54.6 (45–64)</td>
<td>45 652</td>
<td>51</td>
<td>267</td>
<td>12.1 (1.9–56.6)</td>
<td>45.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>6462</td>
<td>1987–1989</td>
<td>53.9 (45–64)</td>
<td>58 019</td>
<td>18</td>
<td>122</td>
<td>6.5 (1.5–30.2)</td>
<td>69.8</td>
<td></td>
</tr>
<tr>
<td>ATBC</td>
<td>Male</td>
<td>21 141</td>
<td>1984–1988</td>
<td>57.3 (50–69)</td>
<td>121 813</td>
<td>534</td>
<td>1339</td>
<td>13.7 (0.8–62.3)</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1666</td>
<td>1974–1995</td>
<td>51.5 (35–80)</td>
<td>14 605</td>
<td>34</td>
<td>34</td>
<td>8.9 (1.3–35.1)</td>
<td>18.0</td>
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</tr>
<tr>
<td>GPS</td>
<td>Male</td>
<td>1658</td>
<td>1974–1995</td>
<td>51.9 (35–80)</td>
<td>14 365</td>
<td>79</td>
<td>102</td>
<td>20.8 (2.7–72.6)</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1606</td>
<td>1974–1995</td>
<td>51.5 (35–80)</td>
<td>14 450</td>
<td>34</td>
<td>34</td>
<td>8.9 (1.2–35.1)</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>HPFS</td>
<td>Male</td>
<td>41 754</td>
<td>1986–1988</td>
<td>53.4 (39–77)</td>
<td>383 206</td>
<td>421</td>
<td>1273</td>
<td>9.7 (1.0–46.1)</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>81 415</td>
<td>1980–1982</td>
<td>47.1 (35–66)</td>
<td>513 915</td>
<td>97</td>
<td>397</td>
<td>5.6 (0.8–35.0)</td>
<td>31.4</td>
<td></td>
</tr>
<tr>
<td>NHSa</td>
<td>Female</td>
<td>61 706</td>
<td>1986–1988</td>
<td>52.6 (39–66)</td>
<td>607 049</td>
<td>208</td>
<td>696</td>
<td>4.9 (0.9–35.9)</td>
<td>34.2</td>
<td></td>
</tr>
<tr>
<td>VIP</td>
<td>Male</td>
<td>9521</td>
<td>1992–1996</td>
<td>49.1 (39–70)</td>
<td>39 230</td>
<td>38</td>
<td>134</td>
<td>4.4 (0.2–15.8)</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10 555</td>
<td>1992–1996</td>
<td>49.3 (39–70)</td>
<td>43 872</td>
<td>4</td>
<td>23</td>
<td>1.7 (0.1–7.3)</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>WHS</td>
<td>Female</td>
<td>37 272</td>
<td>1992–1995</td>
<td>53.9 (38–89)</td>
<td>190 755</td>
<td>10</td>
<td>152</td>
<td>3.7 (0.9–28.4)</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>79 291</td>
<td>1974–1996</td>
<td>54.0 (35–80)</td>
<td>604 266</td>
<td>1123</td>
<td>3115</td>
<td>9.6 (0.9–50.4)</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>199 076</td>
<td>1974–1996</td>
<td>50.4 (35–89)</td>
<td>1 428 216</td>
<td>371</td>
<td>1424</td>
<td>4.7 (0.8–35.0)</td>
<td>33.9</td>
<td></td>
</tr>
</tbody>
</table>

*Sample size after exclusion of participants with baseline cardiovascular diseases, cancers, diabetes mellitus, and missing information on alcohol intake.
+Median values were calculated for drinkers only.

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Table 2. Baseline Characteristics of Women in the Pooled Cohort According to Daily Alcohol Intake

<table>
<thead>
<tr>
<th>Alcohol Intake, g/d</th>
<th>Total</th>
<th>Nondrinkers</th>
<th>0.1–4.9</th>
<th>5.0–14.9</th>
<th>15.0–29.9</th>
<th>30.0–59.9</th>
<th>≥60.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>n*</td>
<td>192 067</td>
<td>65 121</td>
<td>67 187</td>
<td>39 177</td>
<td>12 258</td>
<td>7418</td>
<td>906</td>
</tr>
<tr>
<td>CHD events, n</td>
<td>1385</td>
<td>596</td>
<td>390</td>
<td>241</td>
<td>65</td>
<td>58</td>
<td>15</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>50.4 (7.6)</td>
<td>51.0 (7.7)</td>
<td>49.8 (7.7)</td>
<td>50.1 (7.5)</td>
<td>50.5 (7.4)</td>
<td>51.1 (7.3)</td>
<td>51.3 (7.2)</td>
</tr>
<tr>
<td>Education, low, n (%)†</td>
<td>44 513 (23)</td>
<td>11 971 (18)</td>
<td>14 547 (22)</td>
<td>10 454 (27)</td>
<td>3628 (30)</td>
<td>3426 (46)</td>
<td>487 (54)</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>25.0 (4)</td>
<td>21.8 (3)</td>
<td>19.2 (4)</td>
<td>15.6 (5)</td>
<td>12.8 (7)</td>
<td>10.3 (9)</td>
<td>7.7 (11)</td>
</tr>
<tr>
<td>Fiber,‡ g/d</td>
<td>15.4 (8.4–25.7)</td>
<td>15.7 (8.5–26.7)</td>
<td>15.9 (8.2–26.1)</td>
<td>15.0 (8.3–24.4)</td>
<td>14.2 (7.8–23.1)</td>
<td>12.2 (7.6–20.4)</td>
<td>10.3 (5.0–18.9)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>35 637 (19)</td>
<td>13 566 (21)</td>
<td>11 695 (17)</td>
<td>6271 (16)</td>
<td>2137 (17)</td>
<td>1695 (23)</td>
<td>273 (30)</td>
</tr>
<tr>
<td>Dyslipidemia, n</td>
<td>20 850 (11)</td>
<td>8389 (13)</td>
<td>6599 (10)</td>
<td>3787 (10)</td>
<td>1217 (10)</td>
<td>731 (10)</td>
<td>127 (14)</td>
</tr>
</tbody>
</table>

Differences in distribution of covariates across levels of alcohol consumption were tested by ANOVA (age, BMI), Kruskal-Wallis (dietary factors), and χ² tests (education, smoking, physical activity, hypertension, and dyslipidemia). All tests showed statistically significant differences (P<0.0001).

*After exclusion of participants with missing information on any of the relevant covariates.
†Defined as less than high school.
‡Energy adjusted.

scale, allowing for delayed entry (left censoring). Absolute risks (incidence rates) describing the scale of CHD according to sex, age, and level of alcohol intake were estimated by means of Poisson regression. Absolute risk differences were calculated, and 90% confidence limits were derived by bootstrap estimation (5000 replications) with the 5th and 95th percentiles of the distribution as the lower and upper limits.

We performed primary analyses considering the risk of CHD in categories of alcohol consumption (0, 0.1 to 4.9, 5.0 to 14.9, 15.0 to 29.9, 30.0 to 59.9, and ≥60.0 g/d in women; 0, 0.1 to 4.9, 5.0 to 14.9, 15.0 to 29.9, 30.0 to 59.9, 60.0 to 89.9, and ≥90.0 g/d in men) both for each individual study and for the pooled cohort. The study population was analyzed separately in the following 3 age groups: 39 to 49.9, 50 to 59.9, and ≥60 years. Age was updated during follow-up, and participants were assigned to the appropriate age category; thus, each person could contribute person-time at risk to >1 age category.

Additional analyses exploring the risk of CHD per alcohol increment (1 g/d) were performed. Alcohol was modeled continuously using second-degree fractional polynomials, thus allowing for a single turning point (the nadir) in the risk function. Following the results of Corrao and others, a model describing the dose-response relationship of alcohol on CHD including both a linear and root-squared term of alcohol was applied.

The P value for the test for trend was obtained by assigning the median value within categories of alcohol intake and using this variable as a continuous variable. SAS statistical package version 9.1 was used for all analyses.

We harmonized the variables of the different studies, and the following set of potential confounders was identified on the basis of the method of causal diagrams as suggested by Greenland and others: educational level (less than high school, high school, more than high school), smoking (never smokers, ex-smokers, and current smokers of 1 to 4, 5 to 14, 15 to 24, or ≥25 cigarettes per day), body mass index (BMI; <18.5, 18.5 to 24.9, 25.0 to 29.9, and ≥30 kg/m²), total energy intake (kcal/d), and energy-adjusted quintiles of cholesterol, dietary fiber, saturated fat, monounsaturated fat, and polyunsaturated fat intake. Physical activity measures varied across the cohorts, measured either according to an energy expenditure score of weekly time spent on various activities during the past year (ARC, HPFS, NHS, VIP, and WHS) or according to the intensity of the average weekly physical activity during the past 12 months (ATBC, GPS). These measures were harmonized to a 5-level variable from 1 (least active) to 5 (most active). In addition, models were stratified by study origin and baseline year to account for differences in follow-up procedures or questionnaire design and period effects. Information on postmenopausal hormone therapy use was unavailable in VIP; therefore, the main analyses for women did not include adjustment for this factor. Sensitivity analyses included measures of self-reported history of physician-diagnosed elevated cholesterol (dyslipidemia) and hypertension (yes/no).

Results

Baseline Characteristics

Baseline characteristics of participants from the 8 included studies are shown in Table 1. In total, the pooled study population comprised 199 076 women and 79 291 men who experienced 1424 and 3115 coronary events during 1 428 216 and 604 266 person-years of follow-up, respectively. Baseline age of participants varied from 35 to 89 years in women and from 35 to 80 years in men with a mean age of 50.4 and 54.0 years, respectively. The proportion of nondrinkers varied substantially between studies from 11.4% to 53.0% in women and from 4.7% to 45.8% in men. Median alcohol intakes varied from 4.4 to 20.8 g/d in men and from 1.7 to 8.9 g/d in women.

Tables 2 and 3 show characteristics of participants included in the pooled cohort according to alcohol consumption. Heavier alcohol intake was associated with higher proportions of smokers, physical inactivity, and hypertension and lower median intakes of fat and fiber; a moderate alcohol intake was associated with the highest median cholesterol intake compared with abstainers and heavy drinkers. In men,
Table 4. Study-Specific and Pooled Hazard Ratios of CHD for Categories of Daily Alcohol Intake for Women

<table>
<thead>
<tr>
<th>Alcohol Intake, g/d</th>
<th>Total</th>
<th>Nondrinkers</th>
<th>Hazard Ratio (95% CI)</th>
<th>Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(CHD &lt; 60)</td>
<td>(CHD = 60)</td>
<td>(CHD &gt; 60)</td>
</tr>
<tr>
<td>0.1–4.9</td>
<td>6406</td>
<td>1.00 (Reference)</td>
<td>0.84 (0.44–1.59)</td>
<td>0.87 (0.42–1.80)</td>
</tr>
<tr>
<td>5.0–14.9</td>
<td>1509</td>
<td>1.00 (Reference)</td>
<td>0.76 (0.33–1.75)</td>
<td>1.10 (0.31–4.23)</td>
</tr>
<tr>
<td>15.0–29.9</td>
<td>79479</td>
<td>1.00 (Reference)</td>
<td>0.73 (0.37–1.42)</td>
<td>0.72 (0.28–1.85)</td>
</tr>
<tr>
<td>30.0–59.9</td>
<td>6083</td>
<td>1.00 (Reference)</td>
<td>0.78 (0.35–1.76)</td>
<td>0.74 (0.29–2.00)</td>
</tr>
<tr>
<td>60.0–89.9</td>
<td>9758</td>
<td>1.00 (Reference)</td>
<td>2.26 (0.92–5.57)</td>
<td>2.17 (0.85–5.56)</td>
</tr>
<tr>
<td>≥90.0</td>
<td>34832</td>
<td>1.00 (Reference)</td>
<td>1.02 (0.60–1.75)</td>
<td>0.81 (0.49–1.35)</td>
</tr>
</tbody>
</table>

Table 5. Baseline Characteristics of Men in the Pooled Cohort According to Daily Alcohol Intake

<table>
<thead>
<tr>
<th>Alcohol Intake, g/d</th>
<th>Total</th>
<th>Nondrinkers</th>
<th>Hazard Ratio (95% CI)</th>
<th>Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(CHD &lt; 60)</td>
<td>(CHD = 60)</td>
<td>(CHD &gt; 60)</td>
</tr>
<tr>
<td>0.1–4.9</td>
<td>6406</td>
<td>1.00 (Reference)</td>
<td>0.84 (0.44–1.59)</td>
<td>0.87 (0.42–1.80)</td>
</tr>
<tr>
<td>5.0–14.9</td>
<td>1509</td>
<td>1.00 (Reference)</td>
<td>0.76 (0.33–1.75)</td>
<td>1.10 (0.31–4.23)</td>
</tr>
<tr>
<td>15.0–29.9</td>
<td>79479</td>
<td>1.00 (Reference)</td>
<td>0.73 (0.37–1.42)</td>
<td>0.72 (0.28–1.85)</td>
</tr>
<tr>
<td>30.0–59.9</td>
<td>6083</td>
<td>1.00 (Reference)</td>
<td>0.78 (0.35–1.76)</td>
<td>0.74 (0.29–2.00)</td>
</tr>
<tr>
<td>60.0–89.9</td>
<td>9758</td>
<td>1.00 (Reference)</td>
<td>2.26 (0.92–5.57)</td>
<td>2.17 (0.85–5.56)</td>
</tr>
<tr>
<td>≥90.0</td>
<td>34832</td>
<td>1.00 (Reference)</td>
<td>1.02 (0.60–1.75)</td>
<td>0.81 (0.49–1.35)</td>
</tr>
</tbody>
</table>

Table 6. Multivariable Multicenter Adjusted Odds Ratios of CHD for Categories of Daily Alcohol Intake for Men

<table>
<thead>
<tr>
<th>Alcohol Intake, g/d</th>
<th>Total</th>
<th>Nondrinkers</th>
<th>Hazard Ratio (95% CI)</th>
<th>Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(CHD &lt; 60)</td>
<td>(CHD = 60)</td>
<td>(CHD &gt; 60)</td>
</tr>
<tr>
<td>0.1–4.9</td>
<td>6406</td>
<td>1.00 (Reference)</td>
<td>0.84 (0.44–1.59)</td>
<td>0.87 (0.42–1.80)</td>
</tr>
<tr>
<td>5.0–14.9</td>
<td>1509</td>
<td>1.00 (Reference)</td>
<td>0.76 (0.33–1.75)</td>
<td>1.10 (0.31–4.23)</td>
</tr>
<tr>
<td>15.0–29.9</td>
<td>79479</td>
<td>1.00 (Reference)</td>
<td>0.73 (0.37–1.42)</td>
<td>0.72 (0.28–1.85)</td>
</tr>
<tr>
<td>30.0–59.9</td>
<td>6083</td>
<td>1.00 (Reference)</td>
<td>0.78 (0.35–1.76)</td>
<td>0.74 (0.29–2.00)</td>
</tr>
<tr>
<td>60.0–89.9</td>
<td>9758</td>
<td>1.00 (Reference)</td>
<td>2.26 (0.92–5.57)</td>
<td>2.17 (0.85–5.56)</td>
</tr>
<tr>
<td>≥90.0</td>
<td>34832</td>
<td>1.00 (Reference)</td>
<td>1.02 (0.60–1.75)</td>
<td>0.81 (0.49–1.35)</td>
</tr>
</tbody>
</table>
alcohol intake of up to 60 g/d and among men with an alcohol intake of up to 90 g/d.

We also performed analyses describing the risk of CHD according to alcohol consumption modeled as a continuous variable (Figure 1). In both men and women, a reduction in CHD risk was observed at low to moderate levels of alcohol. The relative risk of CHD was 0.58 (95% confidence interval [CI], 0.49 to 0.68) in women and 0.69 (95% CI, 0.62 to 0.76) in men with a daily intake of 30 g/d, corresponding to 2 to 3 drinks. Higher levels of alcohol consumption were not associated with any discernible additional protection in women and with only modest protection in men.

Alcohol Consumption and Risk of CHD in Age Strata

We estimated the risks of CHD according to alcohol intake separately for 3 age groups, corresponding to age groups of 50 to 59, 60 to 84, and ≥ 85 years, respectively. In all age groups and for both men and women, a decreased risk of CHD according to alcohol intake was observed but with broader confidence bounds for the youngest age group. The test for interaction between alcohol and age was not statistically significant in either women (P = 0.34) or men (P = 0.25). We also modeled the risk continuously for the different age groups and observed similar shapes of the curves (data not shown).

Incidence rates of CHD in women and men according to alcohol intake and age are displayed in Figure 3. As expected, the incidence of CHD was much lower in the younger compared with older participants. The incidence rates of CHD among female abstainers in the 3 age groups were 11 (95% CI, 1 to 109), 41 (95% CI, 1 to 400), and 103 (95% CI, 9 to 1018) per 100 000, respectively. In male abstainers, the incidence rates were 262 (95% CI, 201 to 343), and 454 (95% CI, 354 to 553) per 100 000 for the 3 age groups, respectively. In all age groups and in both men and women, the incidence rate was lower among participants with a low to moderate alcohol intake compared with abstainers. In women, the incidence rate differences between drinking 0 g/d and 5.0 to 29.9 g/d were 3 (90% CI, 0 to 25), 16 (90% CI, 0 to 111), and 35 (90% CI, 0 to 250). For men, the corresponding incidence rate differences were 45 (90% CI, 8 to 84), 64 (90% CI, 24 to 102), and 89 (90% CI, 44 to 140) per 100 000.

Sensitivity Analyses

Heterogeneity between study-specific effects was assessed by the inclusion of an interaction term between alcohol and study origin under the null hypothesis of no between-study differences in the relative risk of CHD by alcohol intake,1,25 with no sign of heterogeneity detected (P = 0.95 in women, P = 0.12 in men). In addition, comparing pooled risk estimates

Table 5. Study–Specific and Pooled Hazard Ratios of CHD for Categories of Daily Alcohol Intake for Men

<table>
<thead>
<tr>
<th>Study Specific</th>
<th>Hazard Ratio, Nondrinkers (ChD = 623)</th>
<th>Alcohol Intake, g/d</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (CHD = 623)</td>
<td>0.1–4.9 (CHD = 737)</td>
<td>5.0–14.9 (CHD = 751)</td>
</tr>
<tr>
<td>A9FC</td>
<td>5166 1.00 (Reference)</td>
<td>1.16 (0.78–1.71)</td>
<td>1.29 (0.93–1.79)</td>
</tr>
<tr>
<td>ATBC</td>
<td>21 119 1.00 (Reference)</td>
<td>0.86 (0.71–1.03)</td>
<td>0.86 (0.72–1.03)</td>
</tr>
<tr>
<td>GPS</td>
<td>1294 1.00 (Reference)</td>
<td>0.84 (0.53–1.32)</td>
<td>0.54 (0.21–1.38)</td>
</tr>
<tr>
<td>HPFS</td>
<td>36 654 1.00 (Reference)</td>
<td>1.00 (0.85–1.17)</td>
<td>0.75 (0.63–0.88)</td>
</tr>
<tr>
<td>VIP</td>
<td>8486 1.00 (Reference)</td>
<td>0.50 (0.28–0.93)</td>
<td>0.24 (0.11–0.48)</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted*</td>
<td>74 719 1.00 (Reference)</td>
<td>0.95 (0.85–1.06)</td>
<td>0.84 (0.75–0.93)</td>
</tr>
<tr>
<td>Smoking-adjusted†</td>
<td>74 719 1.00 (Reference)</td>
<td>0.94 (0.84–1.05)</td>
<td>0.81 (0.72–0.90)</td>
</tr>
<tr>
<td>Multivariable‡</td>
<td>74 719 1.00 (Reference)</td>
<td>0.96 (0.86–1.08)</td>
<td>0.83 (0.74–0.92)</td>
</tr>
</tbody>
</table>

*Also adjusted for year of baseline questionnaire. †Also adjusted for age and year of baseline questionnaire. ‡Multivariable hazard ratios were adjusted for age, year of baseline questionnaire, smoking, BMI, education, physical activity, energy intake, polyunsaturated fat, monounsaturated fat, saturated fat, fiber, cholesterol intake, and study origin. §Not applicable because of a limited number of cases.
after systematically excluding each study at a time confirmed that no single study strongly influenced the pooled estimates. Hence, the pooled hazard ratios are considered appropriate summaries of the study-specific data. Performing a test for interaction between age (time scale) and alcohol consumption did not yield violations of the proportional-hazards assumption for either women (P=0.10) or men (P=0.22).

Separate analyses were performed for fatal and nonfatal events to examine whether the effect of alcohol on CHD differed according to the severity of the outcome. The results of this analysis did not reveal obvious differences between the 2 measures of outcome, although a tendency toward an elevated risk of fatal CHD was observed for the highest alcohol category in both women and men (data not shown).

To examine the possibility that latent baseline symptoms of CHD might reduce the alcohol intake, thereby biasing the results, we performed analyses in which the first 2 or 4 years after baseline were excluded. This did not attenuate the estimates (data not shown).

Additional analyses for women were performed to examine whether adjustment for postmenopausal hormone replacement therapy had an impact on results. This involved excluding participants with unavailable information on this particular covariate (n=9799, 5% of the study population). In the remaining cohorts, postmenopausal hormone replacement therapy did not appreciably affect the association between alcohol and risk of CHD. In addition, the inclusion of history of hypertension and dyslipidemia as covariates in the model did not affect the risk estimates of CHD according to alcohol consumption. Furthermore, an analysis was performed including the IWHS (n=29 801). This inclusion also did not change the hazard ratios appreciably (data not shown).

A test for interaction between alcohol and smoking was performed to examine whether the estimates of the effect of alcohol on CHD risk differed according to smoking status. Smoking did not modify the association between alcohol and CHD in either men (P=0.79) or women (P=0.14). Additional analyses including nonsmokers only were performed separately for women (n=100 144) and men (n=101 055).

Figure 2. Sex- and age-specific pooled hazard ratios of CHD for categories of daily alcohol intake. Multivariable hazard ratios were adjusted for year of baseline questionnaire, education, smoking, BMI, physical activity, total energy intake, polyunsaturated fat, monounsaturated fat, saturated fat, fiber, and cholesterol intake. n indicates number cases for each sex and age group.
Discussion

In this pooled cohort of 8 prospective studies, we observed a lower risk of CHD among men and women with a light to moderate alcohol intake compared with nondrinkers. This finding was consistent across different age groups without significant variations in dose response.

The current data on the effect of alcohol on CHD in younger adults are sparse. In a study based on the Honolulu Heart Program, the authors compared CHD risk according to conventional risk factors in middle-aged and older men (age, 45 to 93 years). Compared with nondrinkers, they observed a lower risk of CHD among drinkers in middle-aged but not among older participants (≥75 years) and concluded accordingly that the relation between alcohol and CHD weakened with age. The study, however, was limited by the simple categorization of alcohol intake into drinkers or nondrinkers and included men only.10

Several plausible explanations for the lowered risk of CHD among moderate drinkers exist. Among those explanations, the evidence is probably strongest for a mechanism involving alcohol increasing high-density lipoprotein cholesterol and reducing plasma fibrinogen levels, thereby reducing platelet aggregability.7,34 The hypothesized J-shaped relation between alcohol intake and diabetes mellitus could also explain some of the benefit from alcohol intake.35,36 In addition, alcohol has an effect on plasminogen activator inhibitor-1 that would tend to reduce thrombosis.37

Previous studies have suggested that the causes of CHD in younger adults differ from the mechanisms involved with CHD in older persons. Results from the Honolulu Heart Program indicated that the effect of hypertension, BMI, and cholesterol on CHD differed according to age. For instance, the relative risk of CHD in hypertensive men declined from 3.7 in those 45 to 54 years of age to 1.7 in those ≥75 years of age. Similarly, associations between BMI and total cholesterol weakened with advancing age.10 The Coronary Artery Risk in Young Adults (CARDIA) study of men and women 33 to 45 years of age found that alcohol intake was associated with expected dose response between alcohol and high-density lipoprotein cholesterol levels and an inverse relation between alcohol and fibrinogen levels.9 They also observed an increased risk of coronary calcification with greater alcohol consumption. Because coronary calcification is a marker of atherosclerosis, this result in young adults is not consistent with the results of the present study.9

Another aspect of alcohol consumption related to age is drinking patterns. Younger adults may tend to binge drink more often than older persons, which may increase their risk of CHD5,7,9; however, findings from the CARDIA study did not indicate a protective effect of alcohol intake on coronary calcification in younger adults even after the exclusion of binge drinkers.9

Our findings suggest a J-shaped curve in women, but in men, the risk did not increase significantly at high amounts of alcohol. Biomarkers that mediate the association between alcohol and decreased risk of CHD such as high-density lipoprotein and fibrinogen are found to explain a larger proportion of the association among men than among women, which may indicate that alcohol has specific effects on such mediators according to sex.7 Other biological explanations for sex-specific associations include differences in alcohol pharmacokinetics (ie, processing and elimination of alcohol in the body), which depend largely on body composition.38,39 However, because the risk curves of this study were modeled separately for the 2 sexes, comparisons between them are not straightforward.

The present study is one of only a few existing studies focusing on the effects of alcohol on CHD according to age. Our work was based on a large body of data with thorough measurements of alcohol intake and relevant covariates. A strength was the availability of diet data in the Pooling Project of Diet and Coronary Disease that enabled adjustment for potential dietary confounders. The size of the study population allowed us to perform subset analyses exploring the association between alcohol and CHD in strata of younger men and women, aspects that even large individual cohorts do not have the power to address. The findings of the present study were strengthened by the prospective design, which provided information on the sequence of events allowing for conclusions on causality, assuming proper confounding control. Potential confounders of the association between alcohol and CHD were carefully selected on the basis of directed
acyclic graphs, ensuring a minimally sufficient set of covariates. Furthermore, the inclusion criteria of the Pooling Project of Diet and Coronary Disease enabled adjustment for relevant dietary factors, which most previous studies did not control for. The pooled analyses included both cohorts and intervention studies from North America and Europe, and similar effects were observed across the studies. Finally, an advantage of the Pooling Project is the inclusion of previously unpublished results, thereby reducing the risk of publication bias.

However, several limitations of the study should also be considered. We focused on the importance of the amount of alcohol consumed; however, other aspects of patterns of alcohol intake may be equally important and were not addressed. Our study included only information on current alcohol consumption and confounders at baseline. For this reason, the reference category of abstainers may contain former drinkers who quit because of existing illness, which could cause a moderate alcohol intake to appear more protective than it is. Although several studies that included only lifelong or long-term abstainers in this category have confirmed a protective effect of alcohol even among healthy individuals, the “sick-quitter” hypothesis is relevant in the present context because older age groups may include more abstainers who stopped drinking because of illness (eg, hypertension).

As mentioned, patterns of alcohol consumption (eg, choice of alcohol type and frequency of consumption) may differ considerably with age, which we did not account for. Our findings of protective effects of alcohol on CHD in all examined age groups may indicate that neither the type of alcohol nor the frequency of consumption modifies the influence of alcohol on CHD considerably. However, future research based on observational studies should emphasize other measures of alcohol intake such as frequency of alcohol consumed. Furthermore, cohort studies with information on lifetime alcohol intake or repeated measurements of alcohol intake and potential confounders could contribute valuable insight because changes in alcohol intake over a given period may be of great importance. Additional experimental studies are also needed to expand the knowledge of biological mechanisms.

Furthermore, this study focused only on CHD events. Overall effects of alcohol on all-cause morbidity and mortality must be considered if we are to optimize alcohol guidelines for different age groups of the population. The lower risk of all-cause mortality is expected to be caused mainly by the effects of alcohol on CHD. In this study, a lower risk of CHD was observed in all examined age groups in moderate alcohol consumers compared with abstainers; however, the absolute risk of CHD was rather low in the youngest age group. Thus, considering the increasing contribution of CHD to all-cause mortality with age, it is reasonable to assume that the protective effect of alcohol on all-cause mortality is mostly pronounced in older age groups. This issue has been addressed in a few previous studies indicating that the protective effect of alcohol consumption on mortality in general is confined to middle-aged and older individuals. Unfortunately, information on all-cause mortality was not collected in the database of the Pooling Project of Diet and Coronary Disease.

Conclusions
This study supports current knowledge that alcohol in moderate amounts protects against CHD in both men and women. Our findings further suggest that this effect is also present in younger age groups. However, younger adults are at low risk for CHD, and the beneficial effects obtained by a moderate alcohol intake may be negligible compared with the increased risk of, for instance, traffic accidents and cancer. Recommendations on alcohol intake among younger adults should consider all-cause mortality and morbidity.

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Disclosures
None.

References
The association between alcohol consumption and decreased risk of coronary heart disease is well established, but possible age differences are plausible because of potential pathogenic differences in coronary heart disease events occurring in younger compared with middle-aged or older individuals. We studied these relations in a large population of men and women 35 to 89 years of age at baseline. We observed a lower risk of coronary heart disease among men and women with a light to moderate alcohol intake compared with nondrinkers, and this finding was consistent and of similar size in all age groups. However, the absolute risk of CHD was small in the youngest age group, and risk differences between abstainers and light to moderate alcohol consumers were of negligible size. Therefore, our results provide strong evidence for a lower risk of coronary heart disease among moderate consumers relative to nondrinkers in younger, middle-aged, and older adults; however, considering absolute risks across age groups, younger adults are not likely to benefit from an overall recommendation of moderate alcohol intake.
Alcoholism and alcohol drinking habits predicted from alcohol dehydrogenase genes

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E-mail: jst@niph.dk

Alcohol drinking habits and alcoholism are partly genetically determined. Alcohol is degraded primarily by alcohol dehydrogenase (ADH) wherein genetic variation that affects the rate of alcohol degradation is found in \textit{ADH1B} and \textit{ADH1C}. It is biologically plausible that these variations may be associated with alcohol drinking habits and alcoholism. By genotyping 9080 white men and women from the general population, we found that men and women with \textit{ADH1B} slow vs fast alcohol degradation drank more alcohol and had a higher risk of everyday drinking, heavy drinking, excessive drinking and of alcoholism. For example, the weekly alcohol intake was 9.8 drinks (95\% confidence interval (CI): 9.1–11) among men with the \textit{ADH1B} /\textit{C1}1/1 genotype compared to 7.5 drinks (95\% CI: 6.4–8.7) among men with the \textit{ADH1B} /\textit{C1}1/2 genotype, and the odds ratio (OR) for heavy drinking was 3.1 (95\% CI: 1.7–5.7) among men with the \textit{ADH1B} /\textit{C1}1/1 genotype compared to men with the \textit{ADH1B} /\textit{C1}1/2 genotype. Furthermore, individuals with \textit{ADH1C} slow vs fast alcohol degradation had a higher risk of heavy and excessive drinking. For example, the OR for heavy drinking was 1.4 (95\% CI: 1.1–1.8) among men with the \textit{ADH1C}1/2 genotype and 1.4 (95\% CI: 1.0–1.9) among men with the \textit{ADH1B} /\textit{C1}2/2 genotype, compared with men with the \textit{ADH1C}1/1 genotype. Results for \textit{ADH1B} and \textit{ADH1C} genotypes among men and women were similar. Finally, because slow \textit{ADH1B} alcohol degradation is found in more than 90\% of the white population compared to less than 10\% of East Asians, the population attributable risk of heavy drinking and alcoholism by \textit{ADH1B} /\textit{C1}1/1 genotype was 67 and 62\% among the white population compared with 9 and 24\% among the East Asian population.

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Keywords: genetic association study; alcoholism; population-based study; alcohol; alcohol dehydrogenase; acetaldehyde

Introduction

Alcoholism and alcohol drinking in general represent huge public health problems in most countries worldwide, preventing many individuals from successfully holding a job or looking after a family. In addition, excessive alcohol use leads to diseases such as liver cirrhosis, chronic pancreatitis, upper gastrointestinal cancers, cardiomyopathy, polyneuropathy and dementia. It has been shown in twin studies that heritability explains approximately 50\% of alcoholism and problem drinking in the white population.\textsuperscript{1,2}

The region surrounding the alcohol dehydrogenase (ADH) gene cluster is known to be associated with alcoholism from whole-genome scans.\textsuperscript{3} Well-known
functional polymorphisms of ADH1B and ADH1C may explain this finding because the ADH1B -2 vs the ADH1B -1 allele confer a 38-fold increase in \textit{in vitro} alcohol degradation rate (that is, the conversion of ethanol to acetaldehyde) and the ADH1C -1 vs the ADH1C -2 allele confer a 2.5-fold increase in \textit{in vitro} alcohol degradation rate.4

During alcohol degradation, acetaldehyde is only found in low concentrations. If concentrations become high, for example, during treatment with disulfiram (used in some countries to prevent alcohol intake among alcoholics) or in individuals with a defective acetaldehyde dehydrogenase (found among Asians), individuals experience severe nausea and flushing and automatically abstain from drinking alcohol. It is possible that similar but less pronounced responses to alcohol are more likely to be produced among individuals carrying the fast alcohol degradation ADH1B -2 and ADH1C -1 alleles compared to individuals carrying the slow alcohol degradation ADH1B -1 and ADH1C -2 alleles. If so, individuals with slow alcohol degradation may be able to drink larger quantities of alcohol without experiencing discomfort due to elevated acetaldehyde levels, and consequently are more likely to use alcohol excessively and to develop alcoholism. This issue has been addressed in different populations in case–control settings where allele frequencies of ADH1B and ADH1C are compared between alcoholics and nonalcoholics.5–28 To our knowledge, this has not been studied in a prospective setting in the general white population and it is unknown if the ADH1B and ADH1C polymorphisms are associated with alcohol drinking habits, such as amount of usual intake.

In the present study, we have genotyped a sample of 9080 men and women from the general white population to test the hypotheses that slow alcohol degradation ADH1B -1 and ADH1C -2 alleles are associated with alcohol drinking habits and with increased risk of alcoholism.

Results

The frequencies of the ADH1B and ADH1C alleles coding for slow alcohol degradation was 0.98 (ADH1B -1) and 0.42 (ADH1C -2) (Table 1). Genotypes were in Hardy–Weinberg equilibrium \( P = 0.8 \) for ADH1B genotypes and \( P = 0.7 \) for ADH1C genotypes by \( \chi^2 \)-test. ADH1B -2 were associated with ADH1C -1 (linkage disequilibrium coefficients \( D' = 0.90 \) and \( r^2 = 0.012 \)).

For ADH1B, we found that men and women who were homozygous for the slow alcohol degrading ADH1B -1 allele had a higher alcohol intake than men and women who were fast alcohol degrading ADH1B -2 heterozygotes or homozygotes. For example, men with the ADH1B -1/1 genotype drank on average 9.8 drinks per week (95% confidence interval (CI): 9.1–11) and men with the ADH1B -1/2 genotype drank on average 7.5 drinks per week (95% CI: 6.4–8.7) (Table 2). Furthermore, odds for any, daily, heavy and excessive alcohol drinking were 2–4 times higher among men and women who were ADH1B -1 homozygotes than among men and women who were ADH1B -2 heterozygotes or homozygotes.

Using the brief Michigan Alcoholism Screening Test (brief MAST) we found that men with the slow alcohol degradation ADH1B -1/1 genotype had a two- to fourfold risk of alcoholism compared to men with the fast alcohol degradation ADH1B -2/1 or ADH1B -2/2 genotypes (Table 2). The hazard ratio of hospitalization for alcoholism in men and women with the slow alcohol degradation ADH1B -1/1 genotype was 3.9 (95% CI: 1.0–16) and 2.7 (95% CI: 0.4–20).

For ADH1C, odds for heavy and excessive alcohol drinking were 40–70% higher among men who were hetero- or homozygous for the slow alcohol degrading ADH1C -2 allele than among men who were homozygous for the fast alcohol degrading ADH1C -1 allele (Table 3). Similar results were found in women; however, effect sizes were slightly smaller and only statistically significant for heavy drinking. ADH1C genotype was not associated with alcoholism (Table 3).

Analyses on daily, heavy and excessive drinking and on alcoholism (MAST score and hospitalizations) were repeated excluding consistent nondrinkers, that is, participants who reported no alcohol intake at every examination in which they participated (7.5% of the total study population). This restriction did not affect any of our results (data not shown).

Because of linkage disequilibrium between the ADH1B -2 and ADH1C -1 alleles, and the relatively large effect on enzyme activity of the ADH1B polymorphism, our results for ADH1C could be influenced by ADH1B genotype. Therefore, ADH1C analyses were repeated solely on individuals who were ADH1B -1 homozygotes (95% of the study cohort): we found similar results, indicating that the effect of ADH1C genotype was independent of ADH1B genotype (data not shown).

We also performed analyses on genotype combinations, ranking genotypes in order of expected total enzyme

<table>
<thead>
<tr>
<th>Table 1 Distribution of ADH1B and ADH1C genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH1B</td>
</tr>
<tr>
<td>1/1 (fast)</td>
</tr>
<tr>
<td>1/1 (slow)</td>
</tr>
<tr>
<td>1/2 (intermediate)</td>
</tr>
<tr>
<td>2/2 (fast)</td>
</tr>
</tbody>
</table>

The Pharmacogenomics Journal
Table 2  Associations between \textit{ADH1B} genotype and alcohol drinking habits and alcoholism

<table>
<thead>
<tr>
<th>\textbf{ADH1B alcohol degradation}</th>
<th>\textbf{Men (n = 4039)}</th>
<th>\textbf{Women (n = 5041)}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/2+2/2 (n = 188) (fast) 1/1 (n = 3851) (slow) 1/2+2/2 (n = 217) (fast) 1/1 (n = 4824) (slow)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol drinking habits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly alcohol intake (n = 3784 M, 4052 W)\textsuperscript{a}</td>
<td>7.5 (6.4–8.7)</td>
<td>9.8 (9.1–11)</td>
</tr>
<tr>
<td>Any alcohol intake (n = 3784 M, 4052 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>2.1 (1.0–4.5)</td>
</tr>
<tr>
<td>Daily drinking (n = 2015 M, 1259 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>2.5 (1.5–4.1)</td>
</tr>
<tr>
<td>Heavy drinking (n = 1262 M, 814 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>3.1 (1.7–5.7)</td>
</tr>
<tr>
<td>Excessive drinking (n = 507 M, 353 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>2.7 (1.1–6.5)</td>
</tr>
<tr>
<td><strong>Alcoholism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bMAST score $\geq$ 5 (n = 351 M, 105 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>2.9 (1.3–6.6)</td>
</tr>
<tr>
<td>bMAST score $\geq$ 10 (n = 217 M, 55 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>2.6 (1.0–7.1)</td>
</tr>
<tr>
<td>Hospitalization (n = 167 M, 74 W)\textsuperscript{c}</td>
<td>1.0 (reference)</td>
<td>3.9 (1.0–16)</td>
</tr>
</tbody>
</table>

Abbreviations: bMAST, the brief Michigan Alcoholism Screening Test; M, men; W, women.

Heavy drinking was defined as drinking more than 21 drinks per week for men and 14 drinks per week for women, and excessive drinking as drinking more than 35 drinks per week for men and 21 drinks per week for women. \textit{n} indicates the number of men and women who are cases in respective analyses. Adjustment was made for \textit{ADH1C} genotype, age, years of school education and examination year.

\textsuperscript{a}Shown numbers are mean number of drinks per week (95% CI), which is estimated among those who report any alcohol intake.

\textsuperscript{b}Shown numbers are OR (95% CI).

\textsuperscript{c}Shown numbers are hazard ratios (95% CI).

Table 3  Associations between \textit{ADH1C} genotype and alcohol drinking habits and alcoholism

<table>
<thead>
<tr>
<th>\textbf{ADH1C alcohol degradation}</th>
<th>\textbf{Men (n = 4039)}</th>
<th>\textbf{Women (n = 5041)}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/1 (n = 1384) (fast) 1/2 (n = 1953) (intermediate) 2/2 (n = 702) (slow) 1/1 (n = 1703) (fast) 1/2 (n = 2428) (intermediate) 2/2 (n = 910) (slow)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol drinking habits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly alcohol intake (n = 3784 M, 4052 W)\textsuperscript{a}</td>
<td>9.8 (9.1–11)</td>
<td>10.4 (9.4–12)</td>
</tr>
<tr>
<td>Any alcohol intake (n = 3784 M, 4052 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>1.3 (0.9–1.8)</td>
</tr>
<tr>
<td>Daily drinking (n = 2015 M, 1259 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>1.1 (0.9–1.4)</td>
</tr>
<tr>
<td>Heavy drinking (n = 1262 M, 814 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>1.4 (1.1–1.8)</td>
</tr>
<tr>
<td>Excessive drinking (n = 507 M, 353 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>1.6 (1.1–2.3)</td>
</tr>
<tr>
<td><strong>Alcoholism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bMAST score $\geq$ 5 (n = 1076 M, 597 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>1.0 (0.8–1.3)</td>
</tr>
<tr>
<td>bMAST score $\geq$ 10 (n = 290 M, 65 W)\textsuperscript{b}</td>
<td>1.0 (reference)</td>
<td>1.0 (0.7–1.3)</td>
</tr>
<tr>
<td>Hospitalization (n = 209 M, 90 W)\textsuperscript{c}</td>
<td>1.0 (reference)</td>
<td>1.2 (0.9–1.7)</td>
</tr>
</tbody>
</table>

Abbreviations: bMAST, the brief Michigan Alcoholism Screening Test; M, men; W, women.

Heavy drinking was defined as drinking more than 21 drinks per week for men and 14 drinks per week for women, and excessive drinking as drinking more than 35 drinks per week for men and 21 drinks per week for women. \textit{n} indicates the number of men and women who are cases in the respective analyses. Adjustment was made for \textit{ADH1B} genotype, age, years of school education and examination year.

\textsuperscript{a}Shown numbers are mean number of drinks per week (95% CI), which is estimated among those who report any alcohol intake.

\textsuperscript{b}Shown numbers are OR (95% CI).

\textsuperscript{c}Shown numbers are hazard ratios (95% CI).
activity, and tested for linear trend in each of the variables for alcohol drinking habits and alcoholism (Figure 1). For most end points, there was a statistically significant trend test in the expected direction: individuals with slow vs fast alcohol degradation drank more alcohol and more often, and had a higher risk of alcoholism.

**Figure 1**  Association between the combined *ADH1B* and *ADH1C* genotypes and alcohol drinking habits and alcoholism. The combined *ADH1B* and *ADH1C* genotypes are ranked according to expected enzyme activity ((*ADH1B*·2/1 + *ADH1B*·2/2, *ADH1C*·1/1) > (*ADH1B*·2/1 + *ADH1B*·2/2, *ADH1C*·2/1 + *ADH1C*·2/2) > (*ADH1B*·1/1, *ADH1C*·1/1) > (*ADH1B*·1/1, *ADH1C*·1/2) > (*ADH1B*·1/1, *ADH1C*·2/2)). *ADH1C*·1/2 and *ADH1C*·2/2 were combined because of few subjects in these categories among the *ADH1B*·2 hetero- and homozygotes. Analyses are for men and women combined and *P*-values are for linear trend tests.

*ADH1B* genotypes are very differently distributed among whites and East Asian populations (Figure 2). Among the white population, more than 90% carry the *ADH1B*·1/1 genotype, coding for slow alcohol degradation, whereas among the East Asian population less than 10% carry this genotype. Hence, the population attributable risk of heavy
Men and women with ADH1B slow vs fast alcohol degradation drank more alcohol, were more often daily, heavy and excessive drinkers and had higher risks of alcoholism. Men and women with ADH1C intermediate and slow vs fast alcohol degradation were more often heavy and excessive drinkers. As expected, effect sizes were smaller for ADH1C than for ADH1B, but given the high frequency of the ADH1C-2 allele, it is nevertheless a very interesting finding. Moreover, the impact of the ADH1C-2 allele on cumulative lifetime alcohol intake may be significant. Our results also suggest that ADH1B and ADH1C genotypes may partly explain why white people generally drink more alcohol than East Asian. The population risk of heavy drinking and alcoholism attributable to the ADH1B-1/1 genotype was 67 and 62% among white population and only 9 and 24% among the East Asian population.

Among men, we found relative estimates for alcoholism from two to three among ADH1B-1 homozygotes, which is comparable to results from a recent meta-analysis consisting predominantly of East Asian studies. Also, the odds ratio (OR) for heavy drinking for men was 3.1 which agrees with what is previously found among Asian men. Separate estimates for women were not available for any of the end points in previous studies. Our results were remarkably similar for men and women indicating that the investigated associations are not sex-specific.

The various end points were probably subject to some misclassification, that is, sensitivity and/or specificity less than 100%. Measures of heavy and excessive drinking will be misclassified if amount of alcohol intake is under- or overreported, which it in many instances probably is. The MAST score is not a perfect screenings tool for alcoholism either. However, these errors occur most likely independently of genotype, and because end points are binary, will lead to bias toward the null. Hence, we do not consider misclassification of end points to have caused our results. For alcoholism defined by hospital registry information, sensitivity is likely considerably less than 100% because many alcoholics are untreated or treated at private clinics that are not included in the national registers. However, specificity could be close to perfect; few nonalcoholics are presumably diagnosed as alcoholics. In this scenario, nondifferential misclassification is not affecting the hazard ratio.

Never-drinkers have not been exposed to alcohol and hence, their drinking status cannot have been affected by ADH1B and ADH1C genotypes. It was not possible to separate never-drinkers from nondrinkers in this study, so performing analyses without never-drinkers was not an option. Potentially, this could have caused bias, but since excluding consistent nondrinkers from analyses had virtually no impact on our results, we do not consider this a major limitation.

We modeled the amount of alcohol intake in five different ways and alcoholism in three different ways. Hence, several statistical tests have been performed which in some instances call for caution. However, outcomes in this study were not independent but merely represent similar

**Discussion**

Our results suggest that ADH1B and ADH1C genotypes are associated with alcoholism and alcohol drinking habits.

![Figure 2](image-url)
outcomes modeled differently and we chose not to adjust for multiple comparisons.

A likely explanation for our findings is that differences in enzyme activity from the ADH1B and ADH1C polymorphisms result in intraindividual differences in alcohol degradation rate and that, for a given level of alcohol intake, individuals with fast alcohol degradation have higher levels of acetaldehyde and thus more unpleasant symptoms compared with individuals with slow alcohol degradation. However, an effect of the polymorphisms on alcohol degradation rate in vivo has been difficult to demonstrate, which may have been due to insufficiently sensitive laboratory methods. In a more recent study which applied a more refined method for measuring the rate of alcohol degradation, results showed a significant difference in degradation rate according to the ADH1B genotype. In further support of an in vivo effect of the ADH1B genotype is that individuals with the most active enzymes are consistently reported to experience more unpleasant symptoms such as flushing when drinking alcohol compared to individuals with the less active enzymatic forms.

Our study had several strengths. First of all, sample size was large and provided adequate power to study associations between the relatively rare ADH1B 1/2 genotype and several end points, and to detect the small effect sizes associated with the ADH1C genotypes. Furthermore, participants were men and women from the general population, all of Danish descent. Hence, population stratification is unlikely to have affected our results. Alcohol drinking habits were described in several dimensions and information on alcoholism was obtained from two independent sources (questionnaire and hospital registry information). All end points were assessed independently from genotyping and participants were unaware of the purpose of this study when enrolled.

In conclusion, our data suggest that alcoholism and alcohol drinking habits are partly predictable from ADH1B and ADH1C genotypes. Results for men and women were comparable and, as expected, effects of ADH1B were larger than effects of ADH1C.

Methods

Study population

Our data originate from The Copenhagen City Heart Study, which is a series of studies conducted in the Danish general population. Examinations consisted of interview and physical examination, and more especially, blood was given for DNA purification at the examination that was performed during 1991–1994. All participants gave written consent and the ethics committee for Copenhagen and Frederiksberg approved the study (no. 100.2039/91). Enrolment and examination procedures have been described in more detail elsewhere. Of the 1780 individuals who were invited to the 1991–1994 examination, 10135 participated, 9259 gave blood and 9222 were successfully genotyped. Eligibility criterion for participation was Danish citizenship and therefore, the Copenhagen City Heart Study does not reflect the ethnic admixture of Copenhagen (the proportion of inhabitants with foreign citizenship was 8% in 1994). However, even a few participants of foreign ethnicity could potentially confound our results since the fast alcohol degradation ADH1B 2 allele is rare among white population and quite frequent in other populations. Information on ethnicity was not assessed at the examinations, and hence information on birthplace was obtained from the Civil Registration System. Participants born in Asia, Africa, the Middle East, South America or Greenland were excluded from further study (n = 211). In all, 9080 individuals were eligible for analyses, some of whom also participated in the examinations during 1981–1983 (n = 6615) and during 2001–2003 (n = 4684).

Genotyping procedures

The ADH1B 2 allele (rs1229984, Arg47His in exon 3) and ADH1C 2 allele (rs699, Ile349Val in exon 8) were identified by means of duplex polymerase chain reaction followed by Nanogen microelectronic chip technology (Nanogen NMW 1000 Nanochip Molecular Biology Workstation) using standard conditions (details available from authors). In a validation study, the accuracy of the Nanogen method was found to be comparable to restriction fragment length polymorphism.

End points

Questions on drinking habits were included in the questionnaire at the examinations during 1981–1983, 1991–1994 and 2001–2003. Amount of alcohol intake was reported as usual intake of weekly beers, wine and spirits. Assuming one drink to be equal to 12 g of pure alcohol, a measure of total weekly intake was calculated. We defined heavy drinking as drinking more than 21 drinks per week for men and 14 drinks per week for women, and excessive drinking as drinking more than 35 drinks per week for men and 21 drinks per week for women. Participants were defined as daily drinkers if they reported to drink alcohol every day.

We defined alcoholism from questionnaire as well as from hospital discharge information. The former definition was taken from the 1991–1994 questionnaire, which included a screening test for alcoholism (10 question version of the brief MAST). The test included questions such as ‘Do you feel you are a normal drinker?’ and ‘Have you ever gone to anyone for help about your drinking?’ Test scores of ≥5 and of ≥10 were used as dichotomized end points. Information on hospitalizations for alcoholism was obtained from the Danish Hospital Discharge Register where all hospitalizations in Denmark, classified according to the World Health Organization’s International Classification of Diseases (ICD) are registered. The following diagnoses indicative of hospitalization due to alcoholism were obtained: ICD-8 codes 303.09–303.99 and ICD-10 codes F10.1–F10.4.

Statistical analyses

All statistical models included ADH1B and ADH1C genotypes, age and years of school education using the SAS/Stat
software (version 8.02). ADH1B-2 heterozygotes were combined with ADH1B-2 homozygotes (n = 6). Estimated haplotype frequencies were calculated by Hplus.46,47 Linkage disequilibrium was expressed as r² and D'.

To study the association between ADH1B and ADH1C genotypes and amount of alcohol intake, the correlated mixed distribution model was applied (Mixcorr macro50). This model handles data with clumping at zero and a lognormal distribution for nonzero values, and contains components to model the probability of a nonzero value and the mean of nonzero values, allowing for repeated measurements using random effects.50 This means that if a variable affects the mean amount by affecting both the probability of occurrence of a nonzero value and the mean of nonzero values, these effects can be separated and quantified. Hence, two estimates are produced from this model: the OR for having a nonzero alcohol intake (that is, for not being a non-drinker) and the mean amount of alcohol intake among those with a nonzero intake.

Risk estimates for alcoholism defined from hospitalizations were computed by means of Cox proportional hazard regression (proc phreg). Age was used as the time axis and models were corrected for delayed entry. Vital status of the participants was obtained from the National Central Person Register. The observation time for each participant was the period from participation in the Copenhagen City Heart Register. The observation time for each participant was the period from participation in the Copenhagen City Heart Register. The observation time for each participant was the period from participation in the Copenhagen City Heart Register. The observation time for each participant was the period from participation in the Copenhagen City Heart Register. The observation time for each participant was the period from participation in the Copenhagen City Heart Register.

Duality of interest
None declared.

References

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
<td>alcohol dehydrogenase</td>
</tr>
<tr>
<td>bMAST</td>
<td>brief Michigan Alcoholism Screening Test</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PAR</td>
<td>population attributable risk</td>
</tr>
<tr>
<td>Ref</td>
<td>Reference group</td>
</tr>
</tbody>
</table>

Acknowledgments
This work was supported by grants from the Danish Graduate School of Public Health, the Health Insurance Foundation, the Ministry of the Interior and Health and the Danish National Board of Health and the Danish Heart Foundation, The Danish Medical Research Council, The Copenhagen County Research Foundation and Chief Physician Johan Boserup and Lise Boserups Foundation. We thank the participants of the Copenhagen City Heart Studies.


Alcohol drinking habits, alcohol dehydrogenase genotypes and risk of acute coronary syndrome

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Abstract

Aims: The risk of myocardial infarction is lower among light-to-moderate drinkers compared with abstainers. Results from some previous studies, but not all, suggest that this association is modified by variations in genes coding for alcohol dehydrogenase (ADH). We aimed to test this hypothesis, including alcohol as both the amount of alcohol and the frequency of drinking. Methods: we conducted a nested case-cohort study within the Danish Diet, Cancer and Health study, including 1,645 men (770 incident cases of acute coronary syndrome from 1993–1997 through 2004 and 875 randomly selected controls). Results: Higher alcohol intake (measured as amount or drinking frequency) was associated with lower risk of acute coronary syndrome; however, there was no evidence that these finding were modified by ADH1B or ADH1C genotypes. Conclusions: The importance of functional variation in alcohol dehydrogenase for the association between alcohol drinking habits and the risk of developing acute coronary syndrome, if any, is very limited.

Key Words: Acute coronary syndrome, alcohol, cohort study, genetic epidemiology

Background

Moderate alcohol intake of approximately 1–2 drinks per day for women and 2–3 drinks per day for men is associated with a lower risk of coronary heart disease [1–4]. It has been suggested that this association is modified by variations in genes coding for alcohol-degrading enzymes: individuals carrying genotypes that code for enzymes giving a slow alcohol degradation may have lower risks for a given level of alcohol intake because they have alcohol in the blood for a longer time period compared with individuals with faster alcohol degradation.

Alcohol degradation is mainly catalyzed by alcohol dehydrogenase (ADH). Different ADHs exist, but the ADH1C gene is especially interesting because of a commonly occurring polymorphism among individuals of Caucasian origin (frequencies of the two alleles are 58% and 42%). In vitro, there is a 2.5-fold difference in activity between the enzymes that are coded at ADH1C1 and ADH1C2 [5,6]. Another alcohol dehydrogenase gene, ADH1B, has two alleles that produce enzymes with a 38-fold difference in alcohol degradation rate [5]. In human studies, however, differences in alcohol degradation rate are much more modest and not even consistently observable [7–12]. In Caucasians, the frequency of the most active allele (ADH1B2) is around 2% [6].

Although results from the first study on the subject indicated that ADH1C slow alcohol degradation was associated with a lower risk of myocardial infarction than ADH1C fast alcohol degradation [13], later results have been less convincing [14–18]. An explanation for this discrepancy could be that the initial
finding was due to chance, because the effect seemingly was confined to one category only, comprising five cases and 37 controls. Another explanation could be that the association between alcohol intake, genotype and heart disease depends upon the drinking pattern: Among individuals who tend to drink large quantities of alcohol at a time, the genotype may be of less importance whereas among individuals with a more frequent drinking pattern, the genotype may be important for the physiological dose of alcohol. A measure of drinking pattern has not been included in any of the previous studies.

In this study, we aim at testing whether the association between alcohol intake and risk of acute coronary syndrome is modified by the \( ADH1B \) or \( ADH1C \) genotypes while taking into account both the amount and frequency of alcohol intake.

Material and methods

The Diet, Cancer and Health Study

During December 1993 to May 1997, 160,725 Danish men and women aged 50 to 65 years were invited by mail to participate in the population-based cohort study Diet, Cancer and Health [19]. Eligible cohort members were born in Denmark, living in the Copenhagen and Aarhus area, and had no previous cancers. A visit at the study clinic was appointed by telephone with people who agreed to participate (27,178 men and 29,875 women (35%)) and a 192-item food frequency questionnaire including questions on amount of alcohol intake was subsequently sent by mail. The food frequency questionnaire was scanned and interviewer-checked during the clinic visit, where another questionnaire concerning lifestyle and background factors, such as smoking habits, physical activity, and education was filled in. Height and weight were also measured at baseline and a blood sample was obtained. A description of the development and validation of the food frequency questionnaire has been published previously [20,21]. The protocol was approved by the Scientific Ethical Committee (KF 01-116/96).

In the food frequency questionnaire, alcohol intake was reported as average (over the preceding year) intake of each beverage: Light, normal and strong beer (in number of bottles); red, white and fortified wine (in number of glasses); and spirits (in number of drinks). The predefined responses were in 12 categories, ranging from “never” to “eight or more per day”. The alcohol content in the different beverage types was defined as one bottle of light beer = 8.9 g ethanol; one bottle of regular beer or one glass of wine = 12.2 g ethanol; one bottle of strong beer = 17.5 g ethanol; one drink of fortified wine = 9.3 g ethanol; and one drink of spirits = 9.9 g ethanol. These categories were converted into number of standard drinks, defined as containing 12 g ethanol, and added to yield an average measure of amount of alcohol intake.

In this study, we aim at testing whether the association between alcohol intake and risk of acute coronary syndrome is modified by the \( ADH1B \) or \( ADH1C \) genotypes while taking into account both the amount and frequency of alcohol intake.

Laboratory analysis

The \( ADH1B:2 \) allele (rs1229984, Arg47His in exon 3) and \( ADH1C:2 \) allele (rs1693482, Arg270Gln in exon 8) were identified by means of Taqman allelic discrimination (ABI 7300, Applied Biosystems). DNA was isolated from frozen lymphocytes [22]. In short, 100 \( \mu \)g DNA were obtained from \( 10^7 \) lymphocytes and 20 ng of DNA were genotyped in 5 \( \mu l \) containing 1 \( \times \) Mastermix (Applied Biosystems, Denmark), 100 nM probes, and 900 nM primers. The case status of the samples was blinded during laboratory analysis. Controls were included in each run, and repeated genotyping of a random 10% subset yielded 100% identical genotypes.

Endpoint and study design

Information on acute coronary syndrome (including unstable angina, non-fatal and fatal myocardial infarction) was obtained by linking the participants (via the unique identification number assigned to all Danish citizens) with central Danish registries of hospital discharge diagnoses and causes of death (ICD-8 codes 410-410.99, 427.27 and ICD-10 codes I20.0, I21.x, I46.x). A case-cohort study was designed using incident validated cases as the endpoint. Cases were identified and verified between baseline and 1 January 2004, the date of the last available update from the Hospital Discharge Register [23]. Consistent with the case-cohort design [24], controls were selected from the entire cohort at random. The present study includes men only, because the number of incident cases among women was not sufficiently high to perform analyses considering alcohol intake and genotype simultaneously. In total, 770 cases of ACS and 875 controls were successfully genotyped and thus constitute the sample for statistical analysis.
Statistical approach

Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between genotype and acute coronary syndrome were estimated using Cox proportional hazard regression with Kalbfleisch and Lawless weights and robust variance estimates suitable for case-cohort data [25]. Age was used as the underlying time axis to ensure that the estimation procedure was based on comparisons of individuals of the same age and hence remove confounding by age. We calculated age-adjusted hazard ratios and hazard ratios adjusted for known risk factors for acute coronary syndrome: Smoking (never, ex-smoker, 1–14, 15–24, or 24+ g tobacco per day), body mass index (BMI, <25, 25–30, 30+ kg/m²), physical activity in leisure time (hours per week), school education (<7, 8–10, or 10+ years in school), fruit (quartiles), vegetables (linearly), fish (linearly), fat (quartiles, % of total energy intake) and saturated fat (% of total energy intake, linearly). Tests for linear trend were performed by treating the median within categories as a continuous variable.

We used the chi-square test to determine whether the \( ADH1B \) and \( ADH1C \) genotypes were in Hardy-Weinberg equilibrium [26]. Tests for interaction were performed by comparing a model including main effects of alcohol and \( ADH1C \) genotypes with a model also including the interaction terms by a log likelihood test i.e. on a multiplicative scale. Analyses were performed using Stata 10.1 (Stata Corp., College Station, TX).

Results

Men who experienced an event of acute coronary syndrome tended to drink less alcohol, to smoke more and to have shorter education (Table I). \( ADH1B \) genotypes were in Hardy-Weinberg equilibrium in the comparison group \( (p = 0.58) \) as well as in the whole sample \( (p = 0.46) \). The same applied for the \( ADH1C \) genotype \( (p = 0.56 \) and 0.29). Allele frequencies were 0.98 (95% CI: 0.97–0.98) \( (ADH1B/1 \text{ slow}) \), 0.02 (95% CI: 0.02–0.03) \( (ADH1B/2 \text{ fast}) \) and 0.61 (95% CI: 0.59–0.62) \( (ADH1C/1 \text{ fast}) \) and 0.39 (95% CI: 0.38–0.41) \( (ADH1C/2 \text{ slow}) \).

Higher alcohol intake was associated with lower risk of acute coronary syndrome: compared with men who drank 1–6 drinks/week, the risk among men who drank 7–20 and 21+ drinks/week was 0.78 (0.59–1.03) and 0.70 (0.51–0.97) \((p \text{ for linear trend} = 0.02)\). Within categories of total alcohol intake, \( ADH1C \) genotypes were not consistently associated with risk of acute coronary syndrome and in particular there was no general tendency that the risk among men with the slow \( ADH1C/2/2 \) genotype was lower than among men with the faster \( ADH1C/1/1 \) or \( ADH1C/1/2 \) genotypes (Table II). Consistent with

Table I. Characteristics by sex and acute coronary syndrome status in 2,667 participants of the Diet, Cancer and Health Study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases ((n = 770))</th>
<th>Controls ((n = 875))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs(^a)</td>
<td>58 (51–65)</td>
<td>56 (51–64)</td>
</tr>
<tr>
<td>Alcohol, drinks/week(^a)</td>
<td>9.7 (0.3–42.2)</td>
<td>11.8 (0.8–48.9)</td>
</tr>
<tr>
<td>(ADH1B) genotype, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/1 (slow)</td>
<td>4.2</td>
<td>4.6</td>
</tr>
<tr>
<td>1/2 (fast)</td>
<td>95.8</td>
<td>95.4</td>
</tr>
<tr>
<td>(ADH1B) genotype, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/1 (fast)</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>1/2 (intermediate)</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>2/2 (slow)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Smokers, % current</td>
<td>59</td>
<td>38</td>
</tr>
<tr>
<td>BMI, kg/m(^2) (^a)</td>
<td>27 (22–34)</td>
<td>26 (22–32)</td>
</tr>
<tr>
<td>Physical Activity, hours/week(^a)</td>
<td>2 (0–11)</td>
<td>2 (0–10)</td>
</tr>
<tr>
<td>Education, % (&lt;7) yrs</td>
<td>46</td>
<td>34</td>
</tr>
<tr>
<td>Vegetables, grams/day(^a)</td>
<td>132 (38–331)</td>
<td>155 (49–373)</td>
</tr>
<tr>
<td>Fruit, grams/day(^a)</td>
<td>124 (17–465)</td>
<td>143 (22–518)</td>
</tr>
<tr>
<td>Saturated fat, % of total energy(^a) intake</td>
<td>13 (6–17)</td>
<td>12 (8–16)</td>
</tr>
<tr>
<td>Fish, grams/day(^a)</td>
<td>41 (12–95)</td>
<td>41 (11–104)</td>
</tr>
</tbody>
</table>

\(^a\)Numbers represent medians (5th and 95th percentiles).

Table II. Hazard ratios\(^a\) 95% confidence intervals of acute coronary syndrome and number of cases by alcohol intake and \( ADH1C \) genotype.

<table>
<thead>
<tr>
<th>Alcohol intake (drinks/week)</th>
<th>1/1 (Fast)</th>
<th>1/2 (Intermediate)</th>
<th>2/2 (Slow)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>0.96 (0.47–1.93) (23)</td>
<td>1.86 (0.94–3.65) (35)</td>
<td>1.45 (0.47–4.47) (10)</td>
</tr>
<tr>
<td>1–6</td>
<td>1 (reference) (79)</td>
<td>1.38 (0.87–2.19) (118)</td>
<td>1.10 (0.59–2.08) (33)</td>
</tr>
<tr>
<td>7–20</td>
<td>0.88 (0.56–1.39) (99)</td>
<td>0.97 (0.62–1.51) (122)</td>
<td>0.91 (0.52–1.58) (45)</td>
</tr>
<tr>
<td>21+</td>
<td>0.97 (0.59–1.59) (84)</td>
<td>0.73 (0.45–1.19) (87)</td>
<td>0.84 (0.46–1.54) (35)</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for smoking, BMI, physical activity, school education, intake of vegetables, fruit, saturated fat and fish. Test for interaction between alcohol intake and \( ADH1C \): \( \chi^2 = 0.35, p = 0.95 \).
this observation, the $p$ value for interaction between alcohol and ADH1C genotype was 0.95. For the ADH1B genotype, the statistical power to perform similar analyses was limited, but results among men drinking seven or more drinks/week did not indicate that ADH1B slow metabolizers were at lower risk than ADH1B fast metabolizers (data not shown). The $p$ value for interaction between alcohol and ADH1B genotype was 0.75.

Higher drinking frequency was associated with a lower risk of acute coronary syndrome among men ($p$ for linear trend $= 0.005$) (Figure 1). Within categories of drinking frequency, the hazard ratios according to the ADH1C genotype were comparable (Figure 2). The $p$ value for interaction between drinking frequency and ADH1C genotype was 0.88. For the ADH1B genotype, there seemed to be no difference in risk of acute coronary syndrome according to drinking frequency either, even though the statistical power was low because of the relatively low frequency of the ADH1B-2 allele (2%) (Table III). The $p$ value for interaction between drinking frequency and ADH1B genotypes was 0.87.

**Discussion**

In this study, we found no evidence that variation in ADH1B and ADH1C genotypes are modifying associations between alcohol intake (amount or drinking frequency) and acute coronary syndrome. A moderate alcohol intake of 1–2 drinks per day for women and 2–3 drinks per day for men is consistently shown to be associated with a decreased risk of coronary heart disease; at higher intakes, there seem to be no further risk reduction and some studies have even reported an increase in risk. In this study cohort, however, no increased risk has been observed even among the most heavy drinkers ($\geq 28$ drinks/week for women and $\geq 35$ drinks/week for men) [27].

Limitations of the present study include that information on alcohol intake was obtained only once; hence it is possible that some participants have changed their alcohol habits during follow-up, resulting in misclassification. However, since information on alcohol intake (and other variables) was collected prospectively, any misclassification is most likely independent of disease status. Also, even though the number of cases was large, we did not have sufficient power to pick up very small effects of the ADH1B and ADH1C genotypes.

Our study had several strengths. The follow-up study design with almost complete follow-up made it unlikely that selection bias affected the study. The outcome information was obtained and validated independently of alcohol intake. Information bias is therefore of no concern. Furthermore, participants were from the general population of Danish descent. Hence, population stratification is unlikely to have affected our results.

If the effect of alcohol on coronary heart disease is modified by variations in ADH genes it really comes down to the question of whether the risk is lower

Table III. Hazard ratios, 95% confidence intervals of acute coronary syndrome and number of cases by alcohol intake and ADH1B genotype.

<table>
<thead>
<tr>
<th>Drinking frequency (days/week)</th>
<th>ADH1B genotype (relative enzyme activity)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>1/2 (Fast)</td>
<td>1/1 (Slow)</td>
</tr>
<tr>
<td></td>
<td>10 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.08 (0.36–3.28) (209)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2+</td>
<td>0.56 (0.15–1.98) (22)</td>
</tr>
<tr>
<td></td>
<td>0.78 (0.26–2.33) (518)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for smoking, BMI, physical activity, school education, intake of vegetables, fruit, saturated fat and fish. Test for interaction between alcohol intake and ADH1B: $\chi^2 = 0.03, p = 0.87$. 
among slow metabolizers than among fast metabolizers for a given level of alcohol intake, because the slow metabolizers may have alcohol in the blood for a longer time period compared with the fast metabolizers. Initially, results in American physicians indicated that this is so [13]. However, this finding was based on only five cases and 37 controls in the highest alcohol drinking category; for a lower alcohol intake there seemed to be no difference in risk of myocardial infarction according to genotype. Another study also found a significant interaction between alcohol and the ADH1C genotype but only after post hoc regrouping of alcohol [14]. In other studies, there was no significant interaction between alcohol and the ADH1C genotype [15–18]. For ADH1B alleles, there is a much larger difference in alcohol degradation rate of the produced enzymes (340 μM/min compared to 9 μM/min) than for enzymes produced by ADH1C alleles (88 μM/min versus 35 μM/min) [9]. We found no indication that the risk of acute coronary syndrome was lower among men with ADH1B slow compared with ADH1B fast alcohol degradation, however, the statistical power to investigate these associations was limited.

In human studies, it has been difficult to demonstrate an effect of the ADH1B variations on the alcohol degradation rate [7], which may be because of insufficiently sensitive laboratory methods – in a recent study where a more refined method for measuring the rate of alcohol degradation was applied, the results showed a significant difference in degradation rate according to the ADH1B genotype [8]. In further support of an in vivo effect of the ADH1B genotype is that individuals with the most active enzymes are consistently reported to experience more unpleasant symptoms such as flushing when drinking alcohol compared with individuals with the less active enzymatic forms [9–12]. For ADH1C variations, similar studies have not been performed, and because of the more limited effect on alcohol degradation rate of ADH1C compared to ADH1B, it is most likely more difficult to observe in vivo effects.

In conclusion, we did not observe any associations between ADH1B or ADH1C genotype and risk of acute coronary syndrome and no interaction between alcohol intake, genotypes and risk of acute coronary syndrome. Hence, our findings do not support the association between alcohol intake and ischaemic heart disease being modified by genetic variation in alcohol degrading enzymes.

Acknowledgements

We would like to thank the participants in the Diet, Cancer and Health Study for their cooperation. Also, we thank Katja Boll for preparing the data file and Anne-Karin Jensen for excellent technical support.

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References


Drinking habits, alcohol genotypes and acute coronary syndrome


Drinking pattern and mortality in middle-aged men and women

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ABSTRACT

Aims To address the prospective association between alcohol drinking pattern and all-cause mortality.


Setting Denmark.

Participants A total of 26,909 men and 29,626 women aged 55–65 years.

Measurements We obtained risk estimates for all-cause mortality for different levels of quantity and frequency of alcohol intake adjusted for life-style factors, including diet.

Findings During follow-up, 1528 men and 915 women died. For the same average consumption of alcohol, a non-frequent intake implied a higher risk of death than a frequent one.

Conclusions Drinking pattern and not just the total amount of alcohol consumed is important for the association between alcohol intake and mortality. These results suggest that future public guidelines concerning sensible alcohol drinking should include messages about drinking pattern together with quantity of alcohol.

KEYWORDS Alcohol drinking, drinking behaviour, follow-up studies, mortality.

INTRODUCTION

A large number of prospective studies have consistently reported a J-shaped relation between an average measure of alcohol intake and all-cause mortality [1–3]. This characteristic form most probably reflects a beneficial effect on the cardiovascular system of light alcohol intake, and harmful implications, such as liver cirrhosis and cancer, of high consumption. These associations have been addressed mainly without taking drinking pattern into account, with the exception of some recent studies [4–10]. Although these studies differed with regard to type and quality of measures of drinking patterns, results implied consistently the importance of drinking pattern in addition to the total quantity consumed. Most recently it has been suggested that drinking frequency, and not the total amount of alcohol, is the primary determinant of the inverse association between alcohol intake and coronary heart disease [8]. However, it seems unlikely that the cardioprotective benefits would outweigh the detrimental effects of a high alcohol intake, regardless of the drinking pattern. Hence, for public health purposes, a more universal outcome such as mortality from all-causes is relevant, because it constitutes a scientific basis for creating guidelines on sensible drinking.

The aim of the present study is to investigate the association between frequency of drinking episodes for a given level of total alcohol consumption and all-cause mortality. We use data from a large prospective cohort study consisting of middle-aged men and women and have the ability to adjust for related life-style factors such as diet and physical activity.
METHODS

During December 1993 to May 1997, 160,725 Danish men and women aged 50–65 years were invited by mail to participate in the population-based study ‘Diet, Cancer and Health’ [11]. Eligible subjects were born in Denmark and had no previous cancers at the time of inclusion. With the invitation, a detailed 192-item food frequency questionnaire including questions concerning average alcohol intake was enclosed. A first visit to the study clinic was arranged by telephone with subjects who agreed to participate [27,178 men and 29,875 women (35%)]. The food frequency questionnaire was returned during the clinic visit, where another questionnaire concerning life-style and background factors including information on frequency of alcohol intake was completed. A description of the food frequency questionnaire has been published previously [12]. The study was conducted in accordance with the Helsinki Declaration II and was approved by the Ethical Committees for the Copenhagen and the Aarhus municipalities (KF 01–116/96).

Alcohol intake and drinking patterns

In the background questionnaire, subjects reported their usual frequency of alcohol intake in seven possible response categories: never drink alcohol, less than once per month, one to three times per month, once a week, two to four times per week, five to six times per week and daily.

In the food frequency questionnaire, participants were asked to state their average quantity (during the last year) of alcohol consumption as the intake of specific amounts of each beverage: light, normal and strong beer (in number of bottles); red, white and fortified wine (in number of glasses); and spirits (in number of drinks). The possible response categories were no alcohol intake, less than one per month, one to three per month, one to three per month, one to four per week, five to six per week, one per day, two to three per day, four to five per day, six to seven per day and eight or more per day. Based on ethanol content in the different beverage types, these categories were converted into number of standard drinks (12 g alcohol) per week and added to yield an average measure of total alcohol intake.

For a given quantity of total alcohol intake, two groups of drinkers were formed to differentiate between individuals drinking little alcohol frequently and individuals consuming a larger quantity of alcohol more rarely. Frequent drinkers were defined as individuals who consumed alcohol at least 2 days per week and non-frequent drinkers were defined as subjects who used to drink alcohol less often. Abstainers were defined as subjects who, in both questionnaires, reported never to drink.

For women, total alcohol intake was categorized into five levels (none, less than one, one to six, seven to 13 and more than 13 drinks per week) and for men, total alcohol intake was categorized into six levels (none, less than one, one to six, seven to 13, 14–20 and more than 20 drinks per week).

Education

In the life-style questionnaire, education was estimated from length of basic schooling as 7 years or less, 8–10 years or 11 years and longer.

Smoking habits

Subjects reported if they were never-smokers, ex-smokers or current-smokers. Current smokers reported number of daily cigarettes, cheroots, cigars and pipes. Assuming one cigarette to be equivalent to 1 g, one cheroot or one pipe to 3 g and one cigar to 5 g tobacco, total amount of smoking was calculated. Two variables were constructed, one indicating smoking status (never, ex, current) and one indicating amount of smoking (0 for never and ex-smokers, and 1–14 g per day, 15–24 g per day or more than 24 g per day for current smokers).

Body mass index

The participants’ height and weight were measured in light clothes and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m) and modelled as linear splines after log-transformation with knots at 18.5, 25, and 30 kg/m². These limits were set in accordance with guidelines from the World Health Organization [13].

Physical activity

Subjects reported if they were physically active during leisure time, including undertaking sports, housework, gardening, taking walks and bicycling. For each activity, a dichotomized variable was computed with the cut-point defined as performing or not performing the activity in question.

Diet

Indicators of a healthy diet among the participants were chosen from the food frequency questionnaire. For intake of fish, cooked vegetables, salad and fruit, respectively, the intake was dichotomized as high or low. The cut-points were defined as close as possible to the 10th percentile of the sex-specific distribution (fish, once a month or less; vegetables, twice per month or less; salad, once a month or less; and fruit, once a week or less). The participants also indicated which type of fat used mainly for cooking
and two groups were formed: the participants in one group who used mainly olive oil and those in another group who used mainly other types of fat for cooking. Use of fat spread on bread was used as a measure of saturated fat intake because one-third of saturated fat intake in Denmark is consumed as spread on bread. Two groups were formed, users and non-users of fat spread on bread.

Diseases before baseline

Information on the participants’ health status when entering the study cohort was obtained from the population-based Danish Patient Register, which keeps records of all somatic hospitalizations in Denmark since 1977. The diagnoses are classified according to the World Health Organization’s International Classification of Diseases, 8th revision (ICD-8). By linking the study cohort to this register, information on the participants’ health status from 1977 to baseline (1993–97) was obtained. Dichotomized variables were constructed for stroke (ICD-8 codes: 430–438), acute myocardial infarction (ICD-8 code: 410), angina pectoris (ICD-8 codes: 411 and 413), other cardiovascular diseases (ICD-8 codes: 390–409, 412, 414–429 and 439–458) and other diagnoses implying diseases with a chronic character. The latter includes infectious, endocrinological, nervous system, chronic lung, gastrointestinal, alcohol-related, urological and muscular diseases (ICD-8 codes: 40–44, 79–83, 93–95, 240–289, 340–358, 490–493, 530–537, 560–573, 577, 580–584 and 710–738).

Follow-up

Vital status of the study population sample was followed until 20 February 2003 by using the unique person identification number in the Civil Registration System. The observation time for each participant was the period from enrolment into the study (December 1993 to May 1997) until 20 February 2003, death (n = 2443), emigration (n = 255) or disappearance (n = 4), whichever came first.

Statistical analysis

Subjects with incomplete information on alcohol intake (n = 104) or on any of the potential confounders (n = 240) were excluded from the analyses. A few subjects had reported conflicting answers between their average total alcohol intake and the frequency of alcohol intake, and as it was difficult to categorize such subjects they were excluded from the analyses (n = 174). A total of 56535 subjects were eligible for this study.

Pearson’s correlation coefficient was calculated to examine the magnitude of correlation between drinking frequency and amount of drinking.

Risk estimates were computed by means of Cox proportional hazard regression models [14] (SAS/STAT program software). Age was used as the time axis to ensure that the estimation procedure was based on comparisons of individuals at the same age. The analyses were corrected for delayed entry, such that individuals were considered at risk only from the age at entry into the study cohort. In one model (Fig. 1), the frequency of drinking was categorized into two levels (subjects consuming alcohol at least 2 days per week and subjects consuming alcohol less often) for each level of total alcohol intake. In another model (Table 1a,b), the frequency of drinking was categorized into four levels (once per week or less, two to four times per week, five to six times per week and daily drinking) for every level of total alcohol intake. For each model, all combinations of frequency and level of total alcohol intake were entered simultaneously. Having had a diagnosis of a disease before baseline, school education, smoking, BMI, intake of fish, fruit, salad and vegetables, use of olive oil in cooking and of fat on bread were included as covariates in the adjusted model. All analyses were performed for each sex separately. The assumption of proportional hazards in the Cox model was tested for each covariate by evaluating the parallelism of the stratified survival curves graphically and by constructing time-dependent variables for the covariates in question and testing these for statistical significance. No violations were detected. Analyses were repeated after exclusion of subjects with a disease before baseline.

We used the Wald test to examine the joint hypothesis of differences in the hazard ratio for mortality between non-frequent and frequent drinkers for a weekly alcohol intake of more than one drink per week.

RESULTS

Among men who reported to consume any alcohol, 21083 did so at least twice per week while 4450 drank alcohol less frequently (Table 2a). Among alcohol-consuming women, 16659 were frequent drinkers and 8103 were non-frequent drinkers (Table 2b). Among both men and women, the median alcohol consumption was higher among frequent drinkers for each category of total alcohol intake than among the corresponding non-frequent drinkers. Overall, drinking frequency was correlated moderately to amount of drinking [Pearson’s correlation coefficient = 0.70 (women) and 0.63 (men)]. Among both men and women, non-frequent drinkers generally had a lower educational level, were more often smokers, more often obese and eating fewer vegetables and fruit than frequent drinkers.

During a mean follow-up of 6.8 years, 1528 men and 915 women died. The adjusted hazard ratios for non-frequent and frequent drinkers according to total alcohol
Table 1

Adjusted hazard ratios* of all-cause mortality (95% confidence limits) according to quantity and frequency of alcohol intake.

<table>
<thead>
<tr>
<th>Alcohol intake, drinks per week</th>
<th>Frequency of alcohol intake</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abstainers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.31 (0.96–1.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–6</td>
<td>0.61 (0.47–0.79)</td>
<td>0.74 (0.56–0.97)</td>
<td>0.91 (0.50–1.66)</td>
</tr>
<tr>
<td>7–13</td>
<td>0.61 (0.42–0.90)</td>
<td>0.56 (0.43–0.73)</td>
<td>0.51 (0.36–0.73)</td>
</tr>
<tr>
<td>14–20</td>
<td>1.11 (0.62–2.00)</td>
<td>0.61 (0.43–0.87)</td>
<td>0.52 (0.35–0.76)</td>
</tr>
<tr>
<td>21+</td>
<td>1.25 (0.70–2.24)</td>
<td>1.03 (0.76–1.41)</td>
<td>0.68 (0.51–0.92)</td>
</tr>
<tr>
<td></td>
<td>(a) Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(b) Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.62 (1.19–2.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–6</td>
<td>1.05 (0.85–1.30)</td>
<td>0.90 (0.70–1.17)</td>
<td>0.72 (0.32–1.64)</td>
</tr>
<tr>
<td>7–13</td>
<td>1.30</td>
<td>0.94 (0.72–1.24)</td>
<td>0.84 (0.56–1.27)</td>
</tr>
<tr>
<td>14+</td>
<td>2.19</td>
<td>1.06 (1.15–4.17)</td>
<td>1.03 (1.15–4.17)</td>
</tr>
</tbody>
</table>

*Adjusted for education, smoking, BMI, physical activity, diet and diseases before baseline.

Figure 1 Hazard ratios (age-adjusted estimates are represented by broken lines and fully adjusted† estimates by full lines) for all-cause mortality according to quantity and frequency of alcohol intake in men and women‡ (frequent = at least 2 drinking days per week, non-frequent = less than 2 drinking days per week).

†Adjusted for education, smoking, BMI, physical activity, diet and diseases before baseline;
‡reference category is drinkers of less than one but more than zero drinks per week.

*p = value less than 0.05 compared to reference category
intake compared with non-drinkers (drinkers of more than zero but less than one drink per week) were estimated (Fig. 1). The hazard ratios of mortality were higher among non-frequent drinkers than among frequent drinkers for a weekly alcohol intake of more than one drink per week \([P = 0.03 \text{ (men)} \text{ and } P = 0.05 \text{ (women)}\) using the Wald test]. Among non-frequent drinking men, the hazard ratios were 0.61 (95% CI, 0.47–0.79), 0.61 (95% CI, 0.42–0.90), 1.11 (95% CI, 0.62–2.00) and 1.25 (95% CI, 0.70–2.24) for subjects drinking one to six, seven to 13, 14–20 and more than 20 weekly drinks, respectively. Correspondingly, the hazard ratios among frequent drinking men were 0.76 (95% CI, 0.58–0.99), 0.57 (95% CI, 0.44–0.72), 0.61 (95% CI, 0.47–0.80) and 0.83 (95% CI, 0.66–1.04). Among non-frequent drinking women, the hazard ratios were 1.05 (95% CI, 0.85–1.30), 1.31 (95% CI, 0.85–2.01) and 2.19 (95% CI, 1.15–4.17) for subjects drinking one to six, seven to 13 and more than 13 weekly drinks, respectively. Correspondingly, the hazard ratios among frequent drinking women were 0.89 (95% CI, 0.69–1.14), 0.91 (95% CI, 0.72–1.16) and 1.20 (95% CI, 0.96–1.51).

The mortality rate ratios for different combinations of quantity and frequency of alcohol intake were also estimated (Table 1a,b). For men, the lowest risk estimates was for drinking seven to 13 drinks per week distributed 5–6 days per week (0.51 95% CI: 0.36–0.73) and for drinking 14–21 drinks per week distributed on 5–6 days per week (0.52 95% CI 0.35–0.76) (Table 2a). The highest hazard ratios were obtained among men drinking on 1 day per week or more rarely; for this category the hazard ratio was 1.11 (95% CI: 0.62–2.00) for drinking 14–20 drinks per week and 1.25 (95% CI: 0.70–2.24) for drinking more than 20 drinks per week. The hazard ratio for drinking totally 21 or more drinks per week distributed on 7 days per week was 0.84 (95% CI: 0.66–1.06). For women, the lowest risk estimate was for drinking one to six drinks per week distributed on 7 days per week was 0.84 (95% CI: 0.66–1.06). For women, the lowest risk estimate was for drinking one to six drinks per week distributed on 7 days per week (0.72 95% CI: 0.32–1.64) and for drinking seven to 13 drinks per week distributed on 5–6 days per week (0.84 95% CI: 0.56–1.27) (Table 2a). The highest hazard ratios were obtained among women drinking on 1 day per week or more rarely; for this category the hazard ratio was 1.30 (95% CI: 0.85–2.01) for drinking seven to 13 drinks per week distributed on 5–6 days per week.

### Table 2 Baseline characteristics of frequent and non-frequent drinkers according to categories of total alcohol intake.

<table>
<thead>
<tr>
<th>Alcohol intake, drinks per week</th>
<th>Non-frequent</th>
<th>Frequent</th>
<th>Non-frequent</th>
<th>Frequent</th>
<th>Non-frequent</th>
<th>Frequent</th>
<th>Non-frequent</th>
<th>Frequent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men, characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects (n)</td>
<td>3508</td>
<td>2669</td>
<td>741</td>
<td>6981</td>
<td>117</td>
<td>3464</td>
<td>84</td>
<td>7969</td>
</tr>
<tr>
<td>Alcohol intake (median drinks per week)</td>
<td>3.1</td>
<td>4.7</td>
<td>8</td>
<td>9.4</td>
<td>17.6</td>
<td>17.9</td>
<td>27</td>
<td>30.5</td>
</tr>
<tr>
<td>Age (mean years)</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Education (% lowest level)</td>
<td>43</td>
<td>37</td>
<td>45</td>
<td>31</td>
<td>51</td>
<td>31</td>
<td>50</td>
<td>32</td>
</tr>
<tr>
<td>BMI (% more than 30 kg/m²)</td>
<td>21</td>
<td>17</td>
<td>22</td>
<td>16</td>
<td>32</td>
<td>15</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Smoking (% current)</td>
<td>39</td>
<td>33</td>
<td>42</td>
<td>33</td>
<td>44</td>
<td>37</td>
<td>60</td>
<td>47</td>
</tr>
<tr>
<td>Vegetable intake (% in lowest consumption group)</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>13</td>
<td>9</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Fruit intake (% in lowest consumption group)</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>9</td>
<td>8</td>
<td>19</td>
<td>12</td>
</tr>
</tbody>
</table>

| **Women, characteristics**      |             |         |             |         |             |         |             |         |
| Subjects (number)               | 7417        | 5005    | 580         | 6326    | 106         | 5328    |
| Alcohol intake (median drinks per week) | 2.5 | 4.5 | 7.7 | 8.7 | 18.6 | 20.6 |
| Age (mean years)                | 56          | 56      | 57          | 56      | 57          | 56      |
| Education (% lowest level)      | 38          | 27      | 40          | 25      | 42          | 21      |
| Body mass index (% more than 30 kg/m²) | 19 | 14 | 17 | 11 | 18 | 11 |
| Smoking (% current)             | 31          | 26      | 43          | 29      | 55          | 41      |
| Vegetable intake (% in lowest consumption group) | 19 | 16 | 22 | 14 | 23 | 15 |
| Fruit intake (% in lowest consumption group) | 11 | 9 | 12 | 10 | 25 | 18 |

*In addition, 1376 men drank less than one drink per week; †4864 women drank less than one drink per week.
per week and 2.19 (95% CI: 1.15–4.17) for drinking more than 13 drinks per week. The hazard ratio for drinking 14 or more drinks per week distributed on 7 days per week was 1.31 (95% CI: 1.02–1.68). Risk estimates of subjects without diseases before baseline did not differ from the estimates for all subjects (data not shown).

The following covariates were associated independently and positively with mortality for men: having a diagnosis of acute myocardial infarction, angina, other cardiovascular diseases or any chronic disease before baseline, not performing any physical activity, smoking, not eating fruit and salad, not using olive oil for cooking, having a BMI < 18 kg/m² and having school education for less than 11 years. For women, having had a diagnosis of acute myocardial infarction or any chronic disease before baseline, not performing any physical activity, smoking, not eating salad and having a BMI < 18 kg/m² were independently and positively associated with mortality.

**DISCUSSION**

We found that drinking pattern influenced the relation between alcohol intake and all-cause mortality. For the same average consumption of alcohol, a non-frequent intake implied a higher risk of death than a frequent one. However, frequent heavy drinking (>20 drinks per week for men and >13 drinks per week for women) also implied an increased risk of death compared to light drinking. Our study population consisted of middle-aged men and women. This age group constitutes a high-risk population for heart diseases and it is therefore qualified for investigating how the deleterious effects of alcohol are balanced against the protective effect, according to drinking frequency and amount of intake.

The follow-up period in this study was 6.8 years, which is a shorter period than that seen in most other epidemiological studies. This means that the information on alcohol intake given by the participants at baseline probably describes more accurately the actual behaviour of the subjects at follow-up in the present study. The combination of this relatively short follow-up period, the large number of participants and a large variation in frequency and amount of alcohol intake allows us to estimate the hazard ratios for non-frequent and frequent drinkers separately.

The finding that the association between alcohol intake and mortality depends upon drinking pattern has been suggested previously [4–7]. Although other measures of drinking patterns were used, results imply consistently a hazardous effect of drinking alcohol in large amounts per occasion. Most of these studies did not assess drinking pattern over the whole spectrum of total alcohol intake and it was difficult to differentiate between the influence from total alcohol intake and drinking pattern. We avoided the term ‘binge drinking’, which in most studies is defined as drinking a minimum number of drinks per occasion, such as six or 13 [6,7], because the participants were not asked directly about occasional heavy drinking and we can therefore not comment on this with the present data. The drinking pattern in the present study was constructed by combining information on average quantity with usual drinking frequency, as has been performed in some other studies [8,10].

In the present study, covariates were distributed unequally in the two groups of drinkers for most factors and the more ‘unhealthy’ pattern was observed consistently among the non-frequent drinkers (Table 1). Also, Kesse et al. showed that dietary habits are unequally distributed on different categories of alcohol intake [15]. This underlines the importance of a thorough confounder control when addressing alcohol intake and drinking pattern as independent variables. We held information on smoking habits, physical activity, BMI, diet and school education, which provided the possibility to adjust for these potential confounders. To adjust for diet, five presumed indicators of a healthy diet were chosen: intake of fruit, vegetables, saturated fat, plant oil and fish. Adjusting for diet and physical activity reduced the difference in hazard ratios between frequent and non-frequent drinkers and hence the importance of drinking pattern. Possible confounders of our results are social factors, as high volumes of alcohol per occasion have been shown to be associated with negative social circumstances [16]. In the present study, adjustment was made for education, which is expected to correlate strongly with social status. However, more detailed information on other social factors was not accounted for.

Among light drinkers there was little difference in hazard ratios between non-frequent and frequent drinkers. Consequently, the reduced risk of death in light drinkers compared with abstainers seems to depend less on drinking pattern than suggested previously [9]. The beneficial effect of a light alcohol intake on cardiovascular disease has several plausible biological mechanisms, including an increase of serum high-density lipoprotein (HDL) [17], inhibition of platelet production, activation and aggregation [18,19] and increased fibrinolysis [20,21]. The influence of drinking pattern on these mediators has been studied in interventions with moderate to heavy drinkers, where there were no differences in lipid profile or fibrinolysis between weekend and daily drinkers [22,23]. In contrast, non-frequent drinkers had a higher degree of coronary occlusion and a decreased HDL to low-density lipoprotein ratio compared with drinkers with a more regular drinking pattern [24]. The question is whether the latter finding applies to individuals with a light to moderate alcohol intake, especially as another study has shown...
that most light drinkers rarely drink daily and that most daily drinkers are not light drinkers [25].

We used information on mortality from the Civil Registration System, which is updated to 2003. In the future, it will be interesting to include information on cause-specific deaths, but because the follow-up time in the registrers containing this information is much shorter than for the Civil Registration System, it is not yet possible.

The non-frequent drinking pattern compared to frequent drinking involves higher alcohol concentrations in the gastrointestinal tract and in the blood as the non-frequent drinkers consume more alcohol per drinking occasion than do frequent drinkers. This could lead to an enhancement of the harmful effects of alcohol, including alcoholic liver disease and upper gastrointestinal cancers. Wetterling et al. have investigated drinking patterns among alcoholics and found that the occurrence of alcohol-related disorders were more common among subjects with frequent inebriation compared with more continuou drinkers with similar life-time alcohol intake [26]. To our knowledge, the association between drinking pattern and neoplasms in the gastrointestinal tract has not been investigated. Occasional drinking of high consumptions of alcohol is probably also stronger when associated with accidents and suicide, due to increased risk-taking behaviours.

In conclusion, we found that frequency of drinking for moderate and high consumption of alcohol influenced the association between alcohol intake and mortality. At these levels, mortality was higher among non-frequent drinkers compared with frequent drinkers.

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Alcohol Consumption and Risk of Atrial Fibrillation in Men and Women: The Copenhagen City Heart Study
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Alcohol Consumption and Risk of Atrial Fibrillation in Men and Women
The Copenhagen City Heart Study

Kenneth J. Mukamal, MD, MPH, MA; Janne S. Tolstrup, MS; Jens Friberg, MD; Gorm Jensen, MD, DMSc; Morten Grønbæk, MD, PhD, DMSc

Background.—The relationship of the full range of alcohol consumption with risk of incident atrial fibrillation has been inconsistent in previous, mainly case-control studies.

Methods and Results.—In a prospective cohort study, we studied the association between self-reported alcohol use and incident atrial fibrillation among 16 415 women and men enrolled in the Copenhagen City Heart Study. We ascertained use of beer, wine, and spirits individually at up to 3 study visits with a structured questionnaire. We identified cases of atrial fibrillation by routine study ECGs and a validated nationwide registry of all hospitalizations. A total of 1071 cases occurred during follow-up. Among both women and men, alcohol consumption throughout the moderate range was not associated with risk of atrial fibrillation. However, consumption of 35 or more drinks per week among men was associated with a hazard ratio of 1.45 (95% CI 1.02 to 2.04); few women consumed this amount of alcohol. Approximately 5% of cases of atrial fibrillation among men were attributable to heavy alcohol use. Further adjustment for blood pressure and incident coronary heart disease and congestive heart failure did not attenuate the association (hazard ratio 1.63; 95% CI 1.15 to 2.31).

Conclusions.—Heavy alcohol consumption is associated with a higher risk of atrial fibrillation, at least among men. This relationship does not appear to be related to the adverse effects of heavy drinking on coronary heart disease or blood pressure. (Circulation. 2005;112:1736-1742.)

Key Words: alcohol ■ fibrillation ■ arrhythmia ■ epidemiology

Substantial evidence indicates that moderate alcohol consumption is associated with a lower risk of cardiovascular disease than abstention or heavy drinking.1,2 Cohort studies also suggest that moderate alcohol use is inversely associated with risk of congestive heart failure.3,4 However, although anecdotal evidence implicates episodic heavy drinking as a trigger of atrial fibrillation (AF),5 the relationship of the full range of alcohol use with risk of incident AF is less certain.

At least 4 case-control studies have found relatively similar odds of AF among abstainers and moderate drinkers but significantly higher odds of AF among heavier drinkers.6–9 A recent cohort study found a higher risk of AF even among men who consumed =2 drinks per day.10 However, 2 prospective cohort studies have not confirmed this finding.11,12 and Psaty and colleagues12 found that alcohol use was inversely associated with risk of AF in the Cardiovascular Health Study. Moreover, experimental studies suggest that alcohol administration decreases susceptibility to and duration of AF in canine models.13,14 Thus, substantial controversy remains about the relation of alcohol use and risk of AF.

To address the prospective association of alcohol use and risk of AF more fully, we studied more than 16 000 participants of the Copenhagen City Heart Study (CCHS), a population-based cohort study of residents of Copenhagen, Denmark. As part of the study, participants have received routine resting ECGs at 3 examinations, and a national register records diagnoses from all hospitalizations, which provides reliable and valid assessments of incident AF.

Methods

Study Population

The CCHS began in 1976 with an original population sample of 19 698 persons randomly drawn from the Copenhagen Population Register, of whom 14 223 attended an initial examination. After the first examination in 1976 to 1978, this sample (including individuals who did not attend the first examination) was reinvited to participate in 2 more examinations in 1981 to 1983 and in 1991 to 1994. At the second examination in 1981 to 1983, an additional sample of 500...
participants (aged 20 to 24 years) was invited, and at the third examination in 1991 to 1994, a final 3000 subjects (aged 20 to 49 years) were invited. The number of new participants was 14,223 at the first visit, 1563 at the second, and 2360 at the third, for a total of 18,146 individuals. At each of the 3 examinations, participants completed a questionnaire concerning their medical history, socioeconomic status, exercise, smoking, and drinking habits. We excluded participants with prevalent AF on their baseline ECG (n = 118); those with self-reported coronary heart disease, stroke, use of cardiac medication, or use of antihypertensives at baseline (n = 1431); and those with missing information on alcohol use (n = 180), which left us with 16,415 participants eligible for analysis.

The CCHS was approved by the Ethics Committee of Copenhagen and Frederiksborg Municipality, Denmark. New and returning participants gave informed consent verbally at the first 2 examinations (ie, up to 1983) and in writing at each subsequent examination.

Assessment of Alcohol Consumption

Participants reported their alcohol use in standardized interviews. They individually reported their intake of beer (in bottles), wine (in glasses), and spirits (in units), with response categories of “never/hardly ever,” “monthly,” “weekly,” or “daily” and number of drinks per day among daily drinkers. As previously described, less than daily intake was estimated from these categories by regression and added to daily intake (of those beverages consumed daily) as needed. In a validation analysis, the age-adjusted correlation coefficients between self-reported alcohol intake and measured levels of HDL cholesterol were 0.20 among men and 0.22 among women (P < 0.001 for both), similar to findings from other representative cohorts.

We classified participants according to their usual weekly intake of alcohol as in previous studies: < 1 serving, 1 to 6 servings, 7 to 13 servings, 14 to 20 servings, 21 to 27 servings, 28 to 34 servings, and ≥ 35 servings. Because of the more limited range of intake among women, their highest category of alcohol intake was ≥ 21 servings per week.

Because intake was queried separately for each alcoholic beverage, we could not determine overall drinking frequency in the entire cohort with certainty. Using the response categories noted, we estimated drinking frequency among the subset of participants who predominately consumed a single beverage type (> 90% of their overall alcohol use).

Determination of AF

Participants underwent a resting 12-lead ECG at each study examination. Each ECG was coded according to the Minnesota coding system by 2 independent coders; in cases of dispute, a third coder settled the disagreement. A physician then reviewed and confirmed all ECGs classified as AF. In a randomly chosen sample representing 10% (817/8170) of patients aged ≥ 65 years with ECGs initially coded without AF, only 2 ECGs (0.02%) were recoded as AF on review.

In addition, the Danish National Hospital Discharge Register records discharge diagnoses from all Danish hospital admissions. We identified first hospitalizations with a diagnosis of AF using International Classification of Diseases, 8th Revision (ICD-8) codes 427.93 and 427.94 through 1993 and International Classification of Diseases, 10th Revision (ICD-10) code I48.9 from 1994 forward. We additionally adjusted for systolic blood pressure and treated hypertension, incident congestive heart failure, and incident coronary heart disease. Heavy alcohol intake has been identified as a risk factor for each of these variables, and all have been associated with risk of AF, which implies that they could explain at least part of an association between alcohol intake and risk of AF. For the latter 2 variables, we used time-varying covariates set to the date of first hospitalization for each diagnosis.

We performed primary analyses using updated measures of alcohol consumption and other covariates, in which we prospectively assessed the risk of AF in between-examination increments, based on determinations of alcohol consumption and other covariates derived from the preceding questionnaire. We assessed the risk associated with individual beverage types in similar fashion. In beverage-specific analyses, we examined the association of individual categories of intake of a given beverage relative to abstention from that beverage while simultaneously adjusting for the standard covariates that we incorporated into other models and for intake of each of the other 2 beverage types. For tests of linear trend, we treated the median value within categories of alcohol intake as a continuous variable. To explore the dose-response relationship further, we also performed regression analyses using linear splines with knots at increments of 3 drinks/wk. We estimated the population-attributable risk related to heavy alcohol intake using standard methods.

Results

Baseline Characteristics

Table 1 shows the characteristics of participants categorized at baseline according to usual alcohol consumption. Individ-
TABLE 1. Characteristics of 16 415 CCHS Participants Free of Clinical Cardiovascular Disease According to Usual Alcohol Consumption

<table>
<thead>
<tr>
<th>Weekly No. of Drinks</th>
<th>&lt;1</th>
<th>1 to 6</th>
<th>7 to 13</th>
<th>14 to 20</th>
<th>21 to 27 (Men)</th>
<th>28 to 34</th>
<th>35+</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td>n=2631</td>
<td>n=3969</td>
<td>n=1461</td>
<td>n=451</td>
<td>n=315</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Weekly intake (in drinks) of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beer</td>
<td>0</td>
<td>0.9</td>
<td>3.7</td>
<td>4.7</td>
<td>7.0</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wine</td>
<td>0</td>
<td>1.2</td>
<td>4.8</td>
<td>5.7</td>
<td>14.0</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liquor</td>
<td>0</td>
<td>0</td>
<td>1.2</td>
<td>1.3</td>
<td>4.6</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y*</td>
<td>56 (33, 73)</td>
<td>50 (25, 68)</td>
<td>48 (26, 69)</td>
<td>49 (31, 69)</td>
<td>50 (33, 68)</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education &lt;8 y, %</td>
<td>61</td>
<td>37</td>
<td>26</td>
<td>30</td>
<td>29</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cohabiting, %</td>
<td>63</td>
<td>71</td>
<td>70</td>
<td>73</td>
<td>65</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever smokers, %</td>
<td>67</td>
<td>72</td>
<td>77</td>
<td>85</td>
<td>85</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.3</td>
<td>23.4</td>
<td>23.0</td>
<td>22.8</td>
<td>23.6</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>161</td>
<td>163</td>
<td>164</td>
<td>164</td>
<td>164</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise intensity, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>26</td>
<td>14</td>
<td>13</td>
<td>20</td>
<td>23</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>54</td>
<td>60</td>
<td>57</td>
<td>54</td>
<td>49</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate</td>
<td>19</td>
<td>25</td>
<td>28</td>
<td>25</td>
<td>26</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>...</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>FEV1, mean % predicted</td>
<td>80.1</td>
<td>81.8</td>
<td>82.0</td>
<td>81.2</td>
<td>81.0</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family Hx CVD, %</td>
<td>33</td>
<td>33</td>
<td>35</td>
<td>39</td>
<td>32</td>
<td>...</td>
<td>...</td>
<td>0.03</td>
</tr>
<tr>
<td>Income in lower tertile, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>n=824</td>
<td>n=1703</td>
<td>n=1799</td>
<td>n=1269</td>
<td>n=609</td>
<td>n=435</td>
<td>n=949</td>
<td></td>
</tr>
<tr>
<td>Weekly intake (in drinks) of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beer</td>
<td>0.1</td>
<td>2.1</td>
<td>7.0</td>
<td>7.4</td>
<td>16</td>
<td>28</td>
<td>35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wine</td>
<td>0</td>
<td>1.7</td>
<td>1.7</td>
<td>3.0</td>
<td>2.1</td>
<td>1.7</td>
<td>1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liquor</td>
<td>0.1</td>
<td>1.0</td>
<td>1.7</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y*</td>
<td>54 (31, 75)</td>
<td>51 (25, 71)</td>
<td>50 (25, 70)</td>
<td>50 (26, 70)</td>
<td>52 (28, 70)</td>
<td>51 (33, 68)</td>
<td>50 (33, 68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education &lt;8 y, %</td>
<td>54</td>
<td>40</td>
<td>37</td>
<td>36</td>
<td>41</td>
<td>44</td>
<td>50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cohabiting, %</td>
<td>71</td>
<td>77</td>
<td>79</td>
<td>77</td>
<td>77</td>
<td>74</td>
<td>68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever smokers, %</td>
<td>83</td>
<td>81</td>
<td>85</td>
<td>89</td>
<td>92</td>
<td>91</td>
<td>93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.2</td>
<td>24.8</td>
<td>25.0</td>
<td>25.1</td>
<td>25.2</td>
<td>25.9</td>
<td>26.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173</td>
<td>175</td>
<td>175</td>
<td>175</td>
<td>175</td>
<td>174</td>
<td>174</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Exercise intensity, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>25</td>
<td>17</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>22</td>
<td>26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>44</td>
<td>44</td>
<td>48</td>
<td>49</td>
<td>48</td>
<td>45</td>
<td>44</td>
<td>0.01</td>
</tr>
<tr>
<td>Moderate</td>
<td>28</td>
<td>34</td>
<td>33</td>
<td>32</td>
<td>32</td>
<td>29</td>
<td>26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>0.42</td>
</tr>
<tr>
<td>FEV1, mean % predicted</td>
<td>79.1</td>
<td>80.7</td>
<td>80.7</td>
<td>80.0</td>
<td>79.3</td>
<td>76.6</td>
<td>78.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family Hx CVD, %</td>
<td>30</td>
<td>27</td>
<td>28</td>
<td>28</td>
<td>33</td>
<td>27</td>
<td>30</td>
<td>0.09</td>
</tr>
<tr>
<td>Income in lower tertile, %</td>
<td>38</td>
<td>25</td>
<td>19</td>
<td>19</td>
<td>17</td>
<td>20</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; Family Hx CVD, family history of cardiovascular disease.

Medians and probability values from Kruskal-Wallis tests are shown for continuous variables, and proportions and probability values from χ² tests are shown for categorical variables.

*Median (5th percentile, 95th percentile).

In the lowest drinking category tended to be older and to have lower income levels, whereas those in the higher drinking categories were more likely to smoke. Women consumed wine in the greatest amount, whereas men chiefly consumed beer. Average Alcohol Consumption and Risk of AF

We documented 1071 cases of incident AF. Of these 1071, 68 were diagnosed by a study ECG, 891 from hospitalization records, and 112 from both sources. In both age- and multivariable-adjusted analyses, the risk of AF was very
similar between abstainers and those who consumed up to 14 drinks per week (Table 2). Among men, we found a higher risk among consumers of 35 or more drinks per week. We did not find a similar risk among women who consumed 21 or more drinks per week, but very few women consumed 28 or more drinks per week (with a total of only 4 cases of AF among such women). Given that 12.5% of men in the CCHS consumed 35 or more drinks per week, we estimate that ≈5% of cases of AF among men were attributable to this level of intake.

In stratified analyses (not shown), we found no evidence of interaction among participants stratified by sex ($P=0.96$), median age (for men, 55.8 years, $P=0.22$; for women, 56.8 years, $P=0.32$), or median body mass index (for men, 25.5 kg/m², $P=0.68$; for women, 24.0 kg/m², $P=0.49$). In all cases, higher risk was generally restricted to men who drank heavily. In exploratory analyses, using linear splines, of the dose-response relationship among men, there appeared to be a threshold relationship similar to that suggested by analyses of alcohol intake in categories. The risk of AF increased notably at a threshold of ≈35 drinks per week, with a relatively flat relationship at lower levels of intake.

**Potential Mediators of the Alcohol-AF Relation**

We assessed a series of potential mediators of the association of heavy alcohol intake with risk of AF, including blood pressure, incident coronary heart disease during follow-up, incident congestive heart failure during follow-up, and all 3. As expected, all 3 were strongly and independently associated with risk of AF. However, adjustment for these factors individually or together had relatively little effect on our results, consistent with the hypothesis that these factors do not mediate the relation of alcohol use and AF. For example, the relative risk of AF among men who consumed 35 or more drinks per week was 1.45 in the basic model (as noted above) and 1.63 (95% CI 1.15 to 2.31) with further adjustment for all 3 factors (Table 2).

Because the association of intake of 28 to 34 drinks per week with risk of AF was stronger after adjustment for mediators, we conducted a post hoc analysis that grouped all men who consumed 28 or more drinks per week. In this analysis, the hazard ratio for drinking 28 or more drinks per week was 1.29 (95% CI 0.95 to 1.77) with multivariable adjustment and 1.50 (95% CI 1.10 to 2.06) after the inclusion of potential mediators. Given the latter hazard ratio, ≈8% of cases of AF among men were attributable to intake of 28 or more drinks per week after adjustment for mediators.

**Exploratory Analyses of Beverage Type and Drinking Frequency**

Table 3 shows results from exploratory beverage type analyses. There were no statistically significant associations identified. It appeared that consumption of 21 or more drinks per week of both beer and spirits tended to be related to higher risk of AF than found with abstinence from these beverages among men.

We found no clear evidence that drinking frequency was related to risk of AF in either women or men (data not shown). This finding was consistent in analyses adjusted for age, for all covariates, and for all covariates with additional adjustment for overall quality of alcohol use.

**Discussion**

In this prospective cohort study, alcohol intake of 35 or more drinks per week was associated with a higher risk of AF, at least among men. Previous studies of the relation of alcohol use and risk of AF have not yielded consistent results. In a case-control study from the UK General Practice Research Database, Ruigomez and colleagues found that physician-reported alcohol use above 42 U per week was associated
with an OR of 2.4, with no evidence for an inverse association at lower levels of consumption. An innovative case-control analysis of the Framingham Study that incorporated person-time contributed to the study found an OR of 1.34 (95% CI 1.01 to 1.78) among consumers of more than 36 g (3 drinks) of alcohol daily but not at lower levels of intake. An analysis of the Diet, Cancer, and Health cohort found 25% to 46% higher risks of AF associated with average intake of \( \geq 20 \) g/d or more among men but not among women.10 In sharp contrast to these studies, Psaty and colleagues12 found alcohol use to be inversely associated with risk of AF in a 3-year follow-up study of the original Cardiovascular Health Study cohort. To the best of our knowledge, ours is the first prospective cohort study to support the findings of earlier case-control studies that suggested a higher risk restricted to heavy drinking.

The one previous study that assessed beverage type found no differences in risk,\(^ {10} \) despite some evidence that antioxidants can modify AF risk. Mihm and colleagues\(^ {26} \) found that patients with AF have higher levels of 2 markers of oxidative stress in right atrial myofibrillar isolates than do patients without AF undergoing cardiac surgery. The same group subsequently found that ascorbate, an antioxidant, alleviated the pacing-induced shortening of the atrial effective refractory period in dogs and that supplemental ascorbate was associated with an adjusted OR of 0.34 (95% CI 0.10 to 1.19) for postoperative AF among patients undergoing CABG surgery.\(^ {27} \) In the present study, only the heaviest level of overall alcohol intake was associated with higher risk, and no single beverage was consumed in sufficient amounts to compare their respective effects at that level of consumption with confidence.

Further studies, and perhaps meta-analyses of existing studies, are needed to clarify this issue.

Heavier drinkers could sustain a higher risk of AF in a few related ways. First, chronic heavy alcohol use itself could affect atrial structure and size as a direct cardiotoxin, an effect suggested in rat models.\(^ {28} \) Second, chronic heavy drinking could have direct proarrhythmic effects. Third, heavier drinkers are likely to have repeated exposure to episodic heavy drinking.

### Table 3: Adjusted Hazard Ratios for Risk of AF According to Updated Consumption of Individual Alcoholic Beverages

<table>
<thead>
<tr>
<th>Weekly No. of Drinks</th>
<th>&lt;1</th>
<th>1 to 6</th>
<th>7 to 13</th>
<th>( \geq 14 ) (Women)</th>
<th>( \geq 14 ) (Men)</th>
<th>( \geq 21 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>272</td>
<td>129</td>
<td>14</td>
<td>8</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>104854</td>
<td>50484</td>
<td>7067</td>
<td>3110</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.04 (0.83–1.30)</td>
<td>0.65 (0.38–1.12)</td>
<td>1.04 (0.51–2.13)</td>
<td>...</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Wine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>316</td>
<td>160</td>
<td>30</td>
<td>17</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>78983</td>
<td>71646</td>
<td>9275</td>
<td>5612</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.95 (0.76–1.19)</td>
<td>1.09 (0.73–1.62)</td>
<td>1.13 (0.68–1.88)</td>
<td>...</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Spirits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>395</td>
<td>92</td>
<td>29</td>
<td>7</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>116140</td>
<td>42229</td>
<td>5454</td>
<td>1692</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.85 (0.65–1.09)</td>
<td>1.11 (0.75–1.65)</td>
<td>1.19 (0.55–2.57)</td>
<td>...</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>123</td>
<td>212</td>
<td>92</td>
<td>52</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>24274</td>
<td>45758</td>
<td>24182</td>
<td>12454</td>
<td>17323</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.12 (0.88–1.42)</td>
<td>1.01 (0.76–1.34)</td>
<td>1.06 (0.75–1.48)</td>
<td>1.27 (0.92–1.74)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Wine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>288</td>
<td>203</td>
<td>37</td>
<td>13</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>53260</td>
<td>58105</td>
<td>7862</td>
<td>3190</td>
<td>1575</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.00</td>
<td>0.85 (0.69–1.05)</td>
<td>0.97 (0.67–1.39)</td>
<td>0.81 (0.45–1.43)</td>
<td>0.99 (0.46–2.13)</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Spirits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>269</td>
<td>220</td>
<td>49</td>
<td>25</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>58027</td>
<td>53766</td>
<td>7592</td>
<td>2766</td>
<td>1842</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.06 (0.86–1.31)</td>
<td>0.92 (0.67–1.28)</td>
<td>1.19 (0.76–1.87)</td>
<td>1.47 (0.85–2.56)</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

Probability values derive from tests of trend. Hazard ratios were adjusted for age, smoking, education, cohabitation, family history of cardiovascular disease, diabetes, income, physical activity, body mass index, FEV1, height, and intake of the other 2 beverages.
drinking (ie, binge drinking), which could increase the risk of triggering a single episode of AF. To support this, porcine models show that acute alcohol administration increases the inducibility of AF, but mainly at very high blood alcohol concentrations. Further, alcohol consumption could cause brief and otherwise asymptomatic episodes of AF to become persistent. A case-crossover study of patients with acute AF could best assess this distinction but would not change the importance of avoiding heavier drinking.

Specific limitations of the present study warrant discussion. As in any observational study, our results could be influenced by differences between participants in factors other than alcohol consumption for which we did not control. For example, we did not have data on dietary factors other than ethanol, although little is known about how such factors affect risk of AF; this limitation may particularly affect beverage type analyses. To have influenced our primary results, any uncontrolled confounder would need to be associated with both alcohol consumption and risk of AF and generally be unrelated to the other covariates in our multivariable models.

Although we relied on self-reported alcohol consumption in this study, the measures used to estimate alcohol consumption have been found to be valid when compared with a formal dietary interview in Danish populations. Furthermore, we found a correlation of alcohol use and HDL cholesterol of the expected magnitude.

We relied on a hospital registry and periodic study-related ECGs to document cases of AF. Because study examinations occurred every 5 to 10 years, it is likely that we missed some cases of AF among participants who were not hospitalized during the follow-up period.

Although the CCHS is a population-based cohort study with a high participation rate, participants are nearly all white, native-born Danish adults. As a result, our results must be generalized to other populations with an appropriate degree of caution.

Although we found that risk of AF appeared to be higher only among consumers of 35 drinks per week, it is difficult to determine the exact nature of the dose-response relationship, especially at high levels of intake that were relatively uncommon, although we explored this with spline analyses that provided similar findings. This was especially true for analyses of individual beverage types, because consumption of any individual beverage was limited in many cases. We also lack power to exclude a modest increase in risk associated with moderate drinking, although our data suggest that there is not a substantially increased risk associated with moderate intake.

In summary, alcohol consumption of 35 or more drinks per week was associated with an increased risk of AF among men in a population-based cohort of more than 16,000 adults. This finding supports the widely held, but rarely examined, clinical observation that heavy alcohol use can lead to AF and confirms the cardiotoxic effects of heavy drinking. Studies on the effects of alcohol use on patients with established AF are still needed.

Acknowledgments

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References


Alcohol Intake, Alcohol Dehydrogenase Genotypes, and Liver Damage and Disease in the Danish General Population

Janne S. Tølstrup, PhD¹, Morten Grønbæk, MD, PhD, DMSc², Anne Tybjærg-Hansen, MD, DMSc³ and Børge G. Nordestgaard, MD, DMSc⁴

OBJECTIVES: We tested the hypothesis that alcohol, alone and in combination with alcohol dehydrogenase (ADH) 1B and ADH1C genotypes, affects liver damage and disease in the general population.

METHODS: Information on alcohol intake and on liver disease was obtained from 9,080 men and women from the Copenhagen City Heart Study. Biochemical tests for the detection of liver damage were specific for alanine aminotransferase (ALT), aspartate aminotransferase (AST)-to-ALT ratio (AST/ALT), γ-glutamyl transpeptidase (γ-GT), albumin, bilirubin, alkaline phosphatase, coagulation factors, and erythrocyte volume.

RESULTS: Increasing alcohol intake was associated with increasing erythrocyte volume, AST/ALT, and levels of ALT, γ-GT, albumin, bilirubin, coagulation factors, and with decreasing levels of alkaline phosphatase. Multifactorially adjusted hazard ratios for alcoholic liver disease overall were 0.9 (95% confidence interval (CI), 0.6–1.4), 1.4 (0.8–2.5), 1.8 (0.9–3.5), and 4.1 (2.5–7.0) for an alcohol intake of 1–13, 14–20, 21–27, and ≥28 drinks per week, respectively, compared with drinking <1 drink per week (P for trend <0.0001); the corresponding hazard ratios for alcoholic liver cirrhosis were 1.7 (0.6–4.7), 2.0 (0.8–7.1), 6.5 (2.0–21), and 13 (4.6–37) (P for trend <0.0001). ADH1B and ADH1C genotypes were not associated with and did not modify the effect of alcohol on biochemical tests or risk of liver disease.

CONCLUSIONS: Increasing alcohol intake from none to low (1–6 drinks per week) through to moderate (7–20 drinks per week) and excessive intake (≥21 drinks per week) leads to stepwise increases in signs of liver damage with no threshold effect, and to an increased risk of liver disease. The minor changes in biochemical tests for low alcohol intake may not account for subclinical liver disease.

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INTRODUCTION

Excessive alcohol intake associates with biochemical signs of liver damage and disease, which has mostly been shown in case–control studies (1). Whether this is also the case for low-to-moderate levels of alcohol intake in individuals in the general population is unknown. Alcohol-related disease, such as liver cirrhosis, may take several years to develop. Intermediate states from a pathologically healthy organ to full-blown disease exist in all ranges, but are often difficult to study in the general population because the disease has not yet manifested itself into clinical symptoms. Biomarkers for liver damage are appealing alternatives, as they are immediate and sensitive measures, objectively evaluating the current state of the organ.

The production of toxic acetaldehyde within cells is believed to be one of the causes of liver damage and disease in response
to alcohol intake (2–4). Alcohol is degraded in the liver to acetaldehyde, which is then further degraded to acetate by the successive actions of alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase. Among Europeans, a common genetic variation affecting alcohol degradation rates is found in \( ADH1B \) and \( ADH1C \) genes (5). Therefore, \( ADH \) genotypes producing enzymes with different velocities of alcohol conversion to acetaldehyde could lead to different intracellular acetaldehyde concentrations in response to alcohol intake, and thus to differences in damage and disease of the liver (6–10).

We tested the hypotheses that alcohol intake, alone and combined with \( ADH1B \) and \( ADH1C \) genotypes, affects biochemical signs of liver damage and risk of liver disease in the general population. For this purpose, we studied 9,080 individuals from the Danish general population, all well characterized with respect to alcohol intake (11).

METHODS

Study population

Our data originate from The Copenhagen City Heart Study, which consists of four consecutive studies conducted in Denmark between 1976 and 1978, 1981 and 1983, 1991 and 1994, and between 2001 and 2003. Participants who had been living in the Copenhagen area for more than 20 years were randomly chosen from the general population. Before visiting the study clinic, participants completed a questionnaire that included questions on alcohol intake and other lifestyle factors. At the clinic visit, physical examinations were carried out and questionnaires were checked for missing information and any uncertainties were clarified. In addition, blood samples were obtained for measuring different biochemical and DNA markers at the 1991–1994 examination. Hence, participants who attended this examination were included in this study. Of 10,135 individuals who participated in this examination (response rate = 61%), 91% donated blood for biochemical and DNA analyses. Participants of Asian or Black descent \((n = 142)\), or with missing questionnaire data \((n = 14)\), were excluded from further study. In all, 9,080 Whites of Danish ethnicity were eligible for this study, some of whom also participated in the examinations between 1976 and 1978 \((n = 6,408)\), 1981 and 1983 \((n = 6,615)\), and between 2001 and 2003 \((n = 4,684)\). All participants gave informed consent and the Ethics Committee for Copenhagen and Frederiksberg approved the study \(#100.2039/91\). Enrollment and examination procedures have been described in more detail elsewhere (12,13).

Variables

The amount of usual alcohol intake was reported as weekly consumption of beer (in bottles), wine (in glasses), and spirits (in units). Assuming one drink to be equal to 12 g of pure alcohol, a measure of total weekly alcohol intake was calculated. Smoking was reported as the status (never, ex, or current) and amount of smoking (in number of daily cigarettes, cheroots, cigars, and pipes). Assuming one cigarette to be equivalent to 1 g of tobacco, one cheroot or one cigar to be equivalent to 3 g of tobacco, and one pipe to be equivalent to 5 g of tobacco, the total amount of daily smoking was calculated for current smokers. School education was reported as number of years of basic schooling.

Genotyping procedures

The \( ADH1B2 \) allele \((rs1229984, Arg47His\) in exon 3) and \( ADH1C2 \) allele \((rs698, Ile349Val\) in exon 8) were identified by means of a duplex PCR, followed by Nanogen microelectronic chip technology (Nanogen NMW 1000 Nanochip Molecular Biology Workstation (14)) using standard conditions (details available from authors). In a validation study, the accuracy of the Nanogen method was found to be comparable with restriction fragment length polymorphism (15).

Outcome measures

Liver damage. Plasma biochemical tests indicating liver damage (alanine aminotransferase (ALT), aspartate aminotransferase (AST)-to-ALT ratio (AST/ALT), \( \gamma \)-glutamyl transpeptidase \( \gamma \)-GT), albumin, bilirubin, alkaline phosphatase, coagulation factors II, VII, and X, and erythrocyte volume) were used. These were measured using standard hospital assays (Konelab and Boehringer Mannheim) subjected to a daily internal quality control assessing assay precision and a monthly external quality control assessing assay accuracy. For the 1991–1994 examination, AST and albumin were measured immediately after blood was collected and ALT, \( \gamma \)-GT, bilirubin, and alkaline phosphatase were analyzed on plasma frozen at \(-80^\circ C\) for 12–15 years, whereas for the 2001–2003 examination, ALT, \( \gamma \)-GT, albumin, bilirubin, alkaline phosphatase, coagulation factors II, VII, and X, and erythrocyte volume were also analyzed immediately after blood was collected.

Liver disease. Information on diseases of the liver was obtained from the Danish Patient Registry (16) and from the Danish Causes of Death Registry (17), in which all somatic hospitalizations and causes of death are registered for the entire country. Diagnoses are classified according to the World Health Organization’s International Classification of Diseases (ICD), 8th and 10th revision. Vital status of the participants was obtained from the Danish Civil Registration System, wherein information on address and vital status is registered for every Danish citizen. The following diagnoses were obtained: alcohol-induced liver cirrhosis (ICD-8: 571.09 and ICD10: K703) and any alcohol-induced liver disease (ICD-8: 155.09–155.89, 456.00–456.09, 570.00–570.99, 571.09, 571.10–571.99, 573.00–573.09, 785.19–785.39 and ICD10: K70185 C22 R18).

Statistical analysis

Associations between alcohol intake, \( ADH1B \) and \( ADH1C \) genotypes, and biochemical tests were investigated by general linear models. Biochemical tests were log transformed to approximate normal distributions. We used the \( \chi^2 \)-test to
determine whether \(ADH1B\) and \(ADH1C\) genotypes were in the Hardy–Weinberg equilibrium (18). In all analyses, \(ADH1B\)-1/2 was combined with \(ADH1B\)-2/2 because of the low number in the latter group \((n = 5)\).

Risk estimates for liver disease during follow-up were computed by means of Cox proportional hazard regression models. Age was used as the time axis to ensure that the estimation procedure was based on comparisons of individuals of the same age, and hence confounding by age was eliminated. Analyses were corrected for delayed entry. The observation time for each participant was the period from the person’s first participation in the Copenhagen City Heart Study, until date of disease, death from other causes, emigration outside Denmark, or 1 August 2007, whichever came first. Information on independent variables was updated for participants who participated in more than one examination. Assumptions of the proportional hazards models were tested and no violations were detected. Analyses were adjusted for factors known to be associated with alcohol intake, such as age, length of school education \((\leq 7, 8–10, \geq 11\) years), and smoking (never smokers, ex-smokers, current smokers of 1–14, 15–24, >24 g of tobacco per day).

The test for linear trend in the risk estimates for alcohol intake was carried out by treating the median within categories as a continuous variable, and the test for linear trend in \(ADH1C\) genotypes was carried out by coding the genotypes, 0, 1, and 2. Linkage disequilibrium was expressed as \(r^2\) and \(D'\) (19,20).

## RESULTS

### Baseline characteristics

Of the 9,080 participants, 4,039 (44%) were men (Table 1). The mean age was 60 years (10th, 90th percentile = 35, 76) for men and 62 years (10th, 90th percentile = 36, 76) for women. The median alcohol intake was 10 drinks per week (10th, 90th percentile = 0, 32) among men and 3 (10th, 90th percentile = 0, 15) among women, and 53% of the men and 46% of the women were current smokers (Table 1). The frequency of \(ADH1B\) and \(ADH1C\) genotypes coding for the most active enzymes was 4.5 \((ADH1B\)-1/2 + 2/2\) and 34% \((ADH1C\)-1/1\). Both \(ADH1B\) and \(ADH1C\) genotypes were in the Hardy–Weinberg equilibrium \((P = 0.43\) and \(P = 0.64\), respectively). Linkage disequilibrium coefficients Lewontin’s \(D'\) was 0.90 and the correlation coefficient \(r^2\) was 0.01 between \(ADH1B\) and \(ADH1C\), both coding for the fast alcohol degradation enzymatic forms.

### Alcohol intake, ADH genotypes, and liver damage

Increasing amount of alcohol intake was associated with increasing levels of ALT, AST/ALT, \(\gamma\)-GT, albumin (at the 2001–2003 examination only), bilirubin, coagulation factors II, VII, and X, and erythrocyte volume, and with decreasing levels of alkaline phosphatase among both men and women (Figures 1 and 2). \(ADH1B\) and \(ADH1C\) genotypes were not associated with any of these biochemical signs of liver damage (data not shown). \(ADH1B\) and \(ADH1C\) genotypes did not interact with alcohol intake on any of the biochemical signs of liver damage in either gender (all \(P\) values >0.05).

### Alcohol intake, ADH genotypes, and liver disease

Increasing amount of alcohol intake was associated with increasing risk of alcoholic liver disease overall and with alcoholic liver cirrhosis (Table 2). The multifactorially adjusted hazard ratios for alcoholic liver disease overall were 0.9 \((95\%\ CI, 0.6–1.4)\) for a weekly alcohol intake of 1–13 drinks per week, 1.4 \((95\%\ CI, 0.8–2.5)\) for 14–20 drinks per week, 1.8 \((95\%\ CI, 0.9–3.5)\) for 21–27 drinks per week, and 4.1 \((95\%\ CI, 2.5–7.0)\) for 28+ drinks per week, compared with drinking <1 drink per week; the corresponding hazard ratios for alcoholic liver cirrhosis were 1.7 \((95\%\ CI, 0.6–4.7)\), 2.0 \((95\%\ CI, 0.8–7.1)\), 6.5 \((95\%\ CI, 2.0–21)\), and 13 \((95\%\ CI, 4.6–37)\) \((P\ for trend <0.0001)\). \(ADH1B\) and \(ADH1C\) genotypes were not associated with alcoholic liver disease. The association between alcohol intake and liver disease did not seem to be modified by the \(ADH1C\) genotype, as hazard ratios for liver disease were comparable within the strata of the \(ADH1C\) genotype (Figure 3); we did not have enough statistical power to stratify similarly for the \(ADH1B\) genotype. Alcohol intake did

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**Table 1. Characteristics of participants of the Copenhagen City Heart Study 1991–1994 examination**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men ((n = 4,039))</th>
<th>Women ((n = 5,041))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>60 (35, 76)</td>
<td>62 (36, 76)</td>
</tr>
<tr>
<td>Alcohol intake (drinks per week)**</td>
<td>10 (0, 32)</td>
<td>3.0 (0, 15)</td>
</tr>
<tr>
<td><strong>ADH1B genotype (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/1 (slow)</td>
<td>95.4</td>
<td>95.7</td>
</tr>
<tr>
<td>1/2+2/2 (fast)</td>
<td>4.6</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>ADH1C genotype (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/1 (fast)</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>2/1 (intermediate)</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>2/2 (slow)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 years</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>8–10 years</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>≥11 years</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Body mass index (kg/m²)***</td>
<td>26 (22, 31)</td>
<td>24 (20, 31)</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>53</td>
<td>46</td>
</tr>
<tr>
<td>Amount of smoking (g/day)****</td>
<td>20 (7, 30)</td>
<td>15 (5, 21)</td>
</tr>
<tr>
<td>ADH, alcohol dehydrogenase.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Median (10th, 90th percentile). **One drink corresponds to 12 g of pure alcohol. ***Median (10th, 90th percentile), among current smokers only.
not interact with \textit{ADH1B} and \textit{ADH1C} genotypes on the risk of liver disease (all \(P\) values >0.05).

**DISCUSSION**

In this European general population study, we found that increasing alcohol intake from none to low (1–6 drinks per week) through to moderate (7–20 drinks per week) and excessive intake (21+ drinks per week) leads to stepwise increases in signs of liver damage with no threshold effect, and to an increased risk of liver disease. For some of the biochemical tests, only small differences in blood levels between low, moderate, and excessive alcohol intake were observed, and such minor changes may not be indicative of a subclinical damage of the liver. Hence, these findings may only have minor clinical relevance; however, mechanistically, it is nevertheless an interesting finding that levels of these biochemical markers were influenced at very low alcohol intakes with no apparent threshold effect. \textit{ADH1B} and \textit{ADH1C} genotypes were not associated with biochemical signs of liver damage, or with risk of liver disease.

This study and most other studies (6) have not been able to show any effect of \textit{ADH1B} and \textit{ADH1C} genotypes on risk of alcoholic liver disease. Furthermore, in support of this finding, we could not even show the influence of these genotypes on the biochemical signs of liver damage in individuals in the general population.

Increased levels of ALT, AST/ALT, \(\gamma\)-GT, bilirubin, and alkaline phosphatase, and decreased levels of coagulation factors II + VII + X, are generally indicative of acute liver damage (21,22). However, these biochemical tests have never previously been measured in such a large sample from the general population with detailed information on usual alcohol intake. Nevertheless, the increased levels of ALT, AST/ALT, \(\gamma\)-GT, and bilirubin observed in this study in those with the highest alcohol intake is in accordance with that expected, i.e., increased alcohol intake associates with increased biochemical signs of liver cell damage.

Surprisingly, we observed that the amount of alcohol intake was inversely associated with levels of alkaline phosphatase in the general population, which is unlikely to be a chance finding because results were highly significant, consistent in men and women, and observed repeatedly at examinations conducted between 1991 and 1993 and between 2001 and 2003. A possible explanation for this finding is that, although increased alkaline phosphatase values are indicative of acute hepatobiliary tissue damage (21,22), a sustained high intake of alcohol,
possibly leading to mild, clinically undetected chronic pancreatitis with secondary mild biliary obstruction and/or hepatocyte deaths, could reduce the number of cells producing alkaline phosphatase. Mild, clinically unrecognized biliary obstruction could also be the reason for the observed increased bilirubin levels in those in the general population with the highest alcohol intake.

It was also somewhat surprising that increased alcohol intake associated with increased levels of coagulation factors II + VII + X, equivalent to decreased prothrombin time. Chronic damage of hepatocytes by alcohol usually leads to a reduced capacity to produce proteins, such as these coagulation factors and albumin, as seen in alcoholic liver cirrhosis, whereas in less-severe forms of alcoholic liver disease, prothrombin time and thus levels of coagulation factors II + VII + X may not be affected (21,22). However, our observation agrees with previous epidemiological data that heavy alcohol consumption leads to a more procoagulant state with higher levels of coagulation factor VII (23). Alternatively, because albumin also increased in response to increasing alcohol intake, the mechanism behind the increased levels of coagulation factors II + VII + X may be different, but not yet understood, one.

Limitations include the fact that we studied Whites only. Therefore, our results may not necessarily apply to other ethnic groups. Our study had several strengths. First of all, the sample size is large and the wide range of alcohol intake provided enough statistical power to study the effects of low-to-moderate, as well as excessive, alcohol consumption. Furthermore, all participants were men and women from the general population of Danish descent. Hence, population stratification is unlikely to have affected our results.
Table 2. Risk of liver disease according to alcohol intake and ADH1B and ADH1C genotype

<table>
<thead>
<tr>
<th>Alcohol intake (drinks per week)</th>
<th>Sex and age adjusted</th>
<th>Multifactorial adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 (n=1,958)</td>
<td>1.0</td>
<td>0.87</td>
</tr>
<tr>
<td>1–13 (n=4,917)</td>
<td>1.0</td>
<td>0.80</td>
</tr>
<tr>
<td>14–20 (n=857)</td>
<td>2.2 (0.6–7.9)</td>
<td>1.0 (0.8–2.6)</td>
</tr>
<tr>
<td>21–27 (n=746)</td>
<td>7.4 (2.3–23)</td>
<td>1.0 (1.0–3.8)</td>
</tr>
<tr>
<td>≥28 (n=602)</td>
<td>16 (5.5–43)</td>
<td>4.7 (2.8–7.9)</td>
</tr>
</tbody>
</table>

**ADH1B genotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Hazard ratio</th>
<th>P value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1 (n=8,675)</td>
<td>0.9 (0.3–3.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1/2+2/2 (n=405)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**ADH1C genotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Hazard ratio</th>
<th>P value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/2 (n=1,612)</td>
<td>1.2 (0.6–2.5)</td>
<td>0.6 (0.6–1.5)</td>
</tr>
<tr>
<td>2/1 (n=4,381)</td>
<td>1.1 (0.6–2.0)</td>
<td>0.8 (0.8–1.5)</td>
</tr>
<tr>
<td>1/1 (n=3,087)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**ADH1B and ADH1C genotype interaction:**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Hazard ratio</th>
<th>P value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1 (n=8,653)</td>
<td>0.9 (0.3–2.8)</td>
<td>1.0 (0.5–2.3)</td>
</tr>
<tr>
<td>1/2+2/2 (n=402)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**ADH1C genotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Hazard ratio</th>
<th>P value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/2 (n=1,607)</td>
<td>1.2 (0.6–2.5)</td>
<td>0.6 (0.6–1.4)</td>
</tr>
<tr>
<td>2/1 (n=4,371)</td>
<td>1.1 (0.6–2.0)</td>
<td>0.8 (0.8–1.5)</td>
</tr>
<tr>
<td>1/1 (n=3,077)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**ADH1C·2/2 (n=1,612)**

Hence, it is unlikely that these measures are differentially biased according to alcohol intake.

Information on the amount of alcohol was obtained by self-report in a food frequency questionnaire. This method is found to be valid when compared with a formal dietary interview in Danish populations (24,25). Although this comparison does not represent a true validation of frequency questionnaires, dietary interviews are considered to convey more accurate information than frequency questionnaires. Furthermore, the correlation between alcohol and high-density lipoprotein in this cohort is of the expected magnitude (26).

In conclusion, in the general population, increasing alcohol intake leads to increasing signs of liver damage with no threshold effect, and to an increased risk of liver disease. The minor changes in biochemical tests for low alcohol intake may not account for subclinical liver disease.

**CONFLICT OF INTEREST**

Guarantor of the article: Janne S. Tolstrup, PhD.
Specific author contributions: Conception and study design, data analysis and interpretation, and writing the manuscript: Janne S. Tolstrup; conception and study design, data analysis and interpretation, and critical revision of the paper: Morten Grønbæk, Anne Tybjerg-Hansen, and Børge G. Nordestgaard. All authors approved the final version of the paper.

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Potential competing interests: None.

**ACKNOWLEDGMENTS**

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Study Highlights

**WHAT IS CURRENT KNOWLEDGE**

- Excessive alcohol intake is associated with risk of liver damage and disease; however, whether this is also the case for low-to-moderate levels of alcohol intake is unknown.
- The significance of alcohol dehydrogenase (ADH) gene variations for risk of liver damage and disease among Caucasians is unknown, especially for the ADH1B variation, which is unevenly distributed in this population.

**WHAT IS NEW HERE**

- Increasing alcohol intake from none through to moderate and excessive intake leads to stepwise increases in signs of liver damage with no threshold effect, and to an increased risk of liver disease.
- Variations in ADH1B and ADH1C genes is not independently associated with risk of liver damage or with liver disease, and do not seem to modify the effect of alcohol intake on any of these conditions.

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Original Contribution

Risk of Pancreatitis According to Alcohol Drinking Habits: A Population-based Cohort Study

Louise Kristiansen, Morten Grønbæk, Ulrik Becker, and Janne Schurmann Tolstrup

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The association between alcohol intake and pancreatitis has been examined previously in case-control studies, mostly consisting of men. The significance of beverage type and drinking pattern is unknown. The objective of this study was to assess the association between amount, type, and frequency of alcohol intake and risk of pancreatitis. For this purpose, the authors used data on 17,905 men and women who participated in the Copenhagen City Heart Study in 1976–1978, 1981–1983, 1991–1994, and 2001–2003 in Copenhagen, Denmark. Alcohol intake and covariates were assessed by questionnaire. Information on pancreatitis was obtained from national registers. A high alcohol intake was associated with a higher risk of pancreatitis. Hazard ratios associated with drinking 1–6, 7–13, 14–20, 21–34, 35–48, and >48 drinks/week were 1.1 (95% confidence interval (CI): 0.8, 1.6), 1.2 (95% CI: 0.8, 1.8), 1.3 (95% CI: 0.8, 2.1), 1.3 (95% CI: 0.7, 2.2), 2.6 (95% CI: 1.4, 4.8), and 3.0 (95% CI: 1.6, 5.7), respectively, compared with 0 drinks/week (\(P_{trend} < 0.001\)). Associations were similar for men and women. Drinking frequency did not seem to be independently associated with pancreatitis.

Abbreviations: CI, confidence interval; ICD, International Classification of Diseases.

As early as 1878, alcohol was proposed as a risk factor for pancreatitis (1), and it is now considered well known that alcohol increases the risk of pancreatitis. However, epidemiologic studies on the quantitative aspect of the association between alcohol intake and pancreatitis are sparse. To date, only 4 case-control studies (1–4) and 1 ecologic study (5) on this subject have been published. In all these studies, an association was found between alcohol intake and risk of pancreatitis in men; however, only one of the case-control studies included women, where surprisingly, no increased risk of pancreatitis according to alcohol was observed (2). No studies have assessed the risk of pancreatitis associated with other dimensions of alcohol intake, such as beverage type and drinking frequency. It is also uncertain whether a threshold exists, that is, a level of alcohol intake under which the risk of pancreatitis is not increased.

In addition to alcohol, gallstone disease is thought to be an important risk factor for pancreatitis (6) and, because studies indicate that a moderate intake of alcohol could protect against gallstone disease (7, 8), the association between alcohol and risk of pancreatitis might be tempered by gallstone disease.

In this study, we examined the association between alcohol intake and risk of pancreatitis in a large prospective cohort consisting of men and women from the general Danish population. Furthermore, we aimed at addressing whether there may be specific effects of beverage type or drinking frequency and whether the association is mediated by gallstone disease.

MATERIALS AND METHODS

Study population

detail elsewhere (9, 10). Subjects with pancreatitis before baseline or missing information on alcohol intake were excluded, which left 17,905 participants eligible for further analysis. The study was approved by the ethical committees for the Copenhagen area (approval reference number: KF 100.2039/91).

Alcohol intake

Beer, wine, and spirits were categorized as 0, 1–6, 7–13, and ≥14 drinks/week and total alcohol intake as 0, 1–6, 7–13, 14–20, 21–34, 35–48, and >48 drinks per week. Because drinking frequency was assessed separately for beer, wine, and spirits, we could not determine overall drinking frequency with certainty. We performed exploratory analyses defining drinking frequency from a combination of information on beverage type and beverage type-specific drinking frequency, categorizing drinking frequency as rare drinkers, monthly drinkers, weekly drinkers, almost daily drinkers, and daily drinkers.

Covariates

Smoking (never smoker, former smoker, and smoker of 1–14 g, 15–24 g, and ≥24 g of tobacco/day), body mass index (<20, 20–24, and ≥25 kg/m²), physical activity (sedentary, light, moderate, and heavy), school education (<8, 8–11, and ≥11 years of education, corresponding to lower primary school, higher primary school, and secondary school), and income (low, middle, and high income, corresponding to <$30,000, $30,000–$80,000, and >$80,000/year in Denmark in 1991–1994) were considered to be potential confounders. Information on gallstone disease was obtained from the Danish Hospital Discharge Register, which contains data on all hospital admissions in Denmark.

Endpoints

Information on acute and chronic pancreatitis was obtained from the Danish Hospital Discharge Register and the Danish Register of Causes of Death. For acute pancreatitis, the relevant International Classification of Diseases (ICD), Eighth Revision, codes were 577.00–577.04, 577.08, and 577.09, and the ICD, Tenth Revision, code was K85.9. For chronic pancreatitis, the relevant ICD, Eighth Revision, codes were 577.19 and 577.90–577.92, and the ICD, Tenth Revision, codes were K86.0–K86.3, K86.8, and K86.9.

Statistical analysis

Participants accrued person-time from the time of their first participation in the Copenhagen City Heart Study until the time of pancreatitis diagnosis, date of death, emigration, or end of follow-up (July 9, 2007), whichever occurred first. We had follow-up information on 100% of the study participants. Data were analyzed by means of the Cox proportional hazards regression model, with delayed entry implemented by using SAS/STAT, version 9.1, software (SAS Institute, Inc., Cary, North Carolina). Age (in days) was used as the underlying time axis.

Analyses were performed by using updated information on alcohol and covariates. Tests for linear trend were performed by treating the median value within categories of alcohol intake as a continuous variable and adding this to the model. Using fractional polynomials, we performed analyses to study the shape of the risk curve to see if there was any

<table>
<thead>
<tr>
<th>Alcohol Intake, drinks/week</th>
<th>No. of Participants</th>
<th>Beverage Type, % of total intake</th>
<th>Mean Age, years (5th percentile, 95th percentile)</th>
<th>Smoking Status, %</th>
<th>Education, %</th>
<th>Mean Body Index, kg/m²</th>
<th>Physical Inactivity, %</th>
<th>Low Income, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2,953</td>
<td></td>
<td>55 (33, 73)</td>
<td>54</td>
<td>12</td>
<td>62</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>1–6</td>
<td>4,244</td>
<td></td>
<td>49 (25, 68)</td>
<td>57</td>
<td>16</td>
<td>38</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>7–13</td>
<td>1,554</td>
<td></td>
<td>48 (26, 70)</td>
<td>59</td>
<td>18</td>
<td>27</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>14–20</td>
<td>488</td>
<td></td>
<td>50 (31, 69)</td>
<td>67</td>
<td>18</td>
<td>31</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>&gt;20</td>
<td>334</td>
<td></td>
<td>50 (33, 68)</td>
<td>75</td>
<td>11</td>
<td>33</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td></td>
<td>54 (32, 75)</td>
<td>62</td>
<td>22</td>
<td>55</td>
<td>26</td>
<td>25</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>948</td>
<td></td>
<td>50 (25, 71)</td>
<td>62</td>
<td>20</td>
<td>41</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>1–6</td>
<td>1,856</td>
<td></td>
<td>50 (24, 70)</td>
<td>65</td>
<td>20</td>
<td>39</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>7–13</td>
<td>1,989</td>
<td></td>
<td>51 (26, 70)</td>
<td>67</td>
<td>22</td>
<td>37</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>14–20</td>
<td>1,383</td>
<td></td>
<td>51 (30, 69)</td>
<td>75</td>
<td>17</td>
<td>43</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>21–34</td>
<td>1,119</td>
<td></td>
<td>51 (33, 69)</td>
<td>78</td>
<td>16</td>
<td>49</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>35–48</td>
<td>566</td>
<td></td>
<td>50 (24, 67)</td>
<td>84</td>
<td>11</td>
<td>50</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>&gt;48</td>
<td>471</td>
<td></td>
<td>50 (26, 70)</td>
<td>84</td>
<td>11</td>
<td>50</td>
<td>26</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 1. Baseline Characteristics by Alcohol Consumption in 18,035 Danish Men and Women Participating in the Copenhagen City Heart Study, Denmark, 1976–2007
indication of a threshold effect (11). The model with the best fit was a model including alcohol as linear and square terms. To examine the possibility that latent baseline symptoms of pancreatitis might have reduced the amount of alcohol consumed, thereby biasing results, we carried out analyses in which the first 2 or 4 years of observation time were excluded, and information was updated with a delay of 2 or 4 years, respectively.

The test for interaction between alcohol intake and smoking was performed by a nested log likelihood test, comparing a model containing the variables as single terms with a model also including the interaction terms. For this purpose, alcohol was categorized as <7, 7–20, and >20 drinks/week, and smoking was categorized as never smokers, former smokers, and current smokers.

RESULTS

Table 1 shows the characteristics of the 9,573 women and 8,332 men participating in this study, categorized by amount of alcohol intake (assessed on the time of their first participation in the Copenhagen City Heart Study). Among both women and men, those in the higher alcohol categories were more likely to smoke, whereas individuals in the lowest alcohol category tended to be older, to have fewer years of education, and to have lower income levels.

Amount of alcohol intake and risk of pancreatitis

The mean follow-up time in this study was 20.1 years (range, 0–31 years). At the end of follow-up, 235 participants (113 women and 122 men) had developed pancreatitis, and there were 171 cases of acute and 97 cases of chronic pancreatitis.

An increasing risk of pancreatitis according to alcohol intake was observed in both men and women, although this was statistically insignificant in women (data not shown). We performed further analyses including men and women in the same model ($P_{interaction}$ between sex and alcohol in a nested log likelihood test = 0.83). A high alcohol intake was associated with an increased risk of both acute and chronic pancreatitis (Table 2). The hazard ratio for acute and chronic pancreatitis combined (total pancreatitis) increased by 1.13 for every additional drink/day (95% confidence interval (CI): 1.06, 1.21). In multivariate-adjusted models, smoking was responsible for most of the effect of adjustment. The fully adjusted risk of pancreatitis in women compared with men was 0.9 (95% CI: 0.7, 1.2). Including variables for personal income and physical activity in the adjusted model had little effect on risk estimates.

Separating never drinkers from the nondrinkers was not possible in this study, and it is hence possible that the category of nondrinkers contains participants with a previously high intake, resulting in a falsely high incidence rate of pancreatitis in this category. To address this issue, analyses were repeated, separating nondrinkers from consistent nondrinkers, that is, participants who participated in at least 2 examinations and reported no alcohol intake at every examination. During follow-up, 23 cases occurred in the category of consistent nondrinkers. The hazard ratios for total pancreatitis

### Table 2. Risk of Acute Pancreatitis, Chronic Pancreatitis, and Total Pancreatitis According to Updated Consumption of Alcohol Intake, Copenhagen, Denmark, 1976–2007

<table>
<thead>
<tr>
<th>Alcohol Intake, drinks/week</th>
<th>Acute Pancreatitis</th>
<th>Chronic Pancreatitis</th>
<th>Total Pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>0</td>
<td>35</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>1–6</td>
<td>44</td>
<td>1.2</td>
<td>0.7, 2.3</td>
</tr>
<tr>
<td>7–13</td>
<td>48</td>
<td>1.4</td>
<td>0.8, 2.4</td>
</tr>
<tr>
<td>14–20</td>
<td>26</td>
<td>1.8</td>
<td>0.9, 3.6</td>
</tr>
<tr>
<td>21–34</td>
<td>17</td>
<td>2.2</td>
<td>1.0, 4.6</td>
</tr>
<tr>
<td>35–48</td>
<td>13</td>
<td>3.1</td>
<td>0.4, 2.2</td>
</tr>
<tr>
<td>&gt;48</td>
<td>10</td>
<td>4.3</td>
<td>1.7, 11</td>
</tr>
</tbody>
</table>

**P**<0.001  
**P**<0.001  
**P**<0.001

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**a** Adjusted for age and sex  
**b** Adjusted for age, sex, smoking, education, and body mass index.
Using consistent nondrinkers as the reference category were similar to results from the main analysis (data not shown).

Excluding the first 2 or 4 years of observation time revealed results similar to those from the main analyses (data not shown).

Modeling the association between alcohol and risk of total pancreatitis for men and women separately and together, respectively, using fractional polynomials did not indicate that there was a threshold in the risk of pancreatitis according to alcohol (data not shown). The curves flattened out at high intakes, but the test for linearity did not provide evidence for departure from linearity ($P = 0.14$ for women and men combined).

Compared with that among never smokers, the hazard ratio for pancreatitis was 1.6 (95% CI: 1.0, 2.5) among past smokers and 1.5 (95% CI: 0.9, 2.3), 2.3 (95% CI: 1.5, 3.6), and 3.1 (95% CI: 1.8, 5.3) among current smokers of 1–14, 15–24, and $>24$ g of tobacco/day, respectively. We found no evidence of interaction between alcohol intake and smoking ($P = 0.57$).

**Gallstone disease, alcohol, and pancreatitis**

In analyses including gallstone disease as a time-dependent variable, the hazard ratios of pancreatitis according to alcohol were slightly increased: For example, the risk associated with drinking $>48$ drinks/week increased from 3.0 (95% CI: 1.6, 5.7) to 3.6 (95% CI: 1.9, 6.9) when including gallstones in the model. In addition, the hazard ratio for continuous alcohol intake increased from 1.3 (95% CI: 1.06, 1.21) to 1.15 (95% CI: 1.08, 1.23) per drink/day. The hazard ratio of pancreatitis according to gallstone disease was 11 (95% CI: 7.5, 15).

**Analyses of beverage type and drinking frequency**

We explored the relation between type of alcoholic beverage and risk of pancreatitis (Table 3). The adjusted hazard ratio for drinking more than 14 beers/week was 2.0 (95% CI: 1.3, 3.1). No association was observed regarding wine and spirits. However, there were only a few participants in the highest categories of both wine and spirits.

We found no evidence that drinking frequency was associated with risk of pancreatitis. In a comparison with never drinkers, the adjusted hazard ratio was 0.8 (95% CI: 0.5, 1.3), 1.0 (95% CI: 0.7, 1.5), 1.1 (95% CI: 0.6, 1.8), and 1.3 (95% CI: 0.9, 1.9) for monthly, weekly, almost daily, and daily alcohol drinking. With further adjustment for the amount of alcohol intake (as a continuous variable), the hazard ratio for daily drinking attenuated to 1.0 (95% CI: 0.6, 1.5). In this model, amount of alcohol intake remained significantly associated with increased risk of pancreatitis ($P < 0.001$), indicating that amount of alcohol is more important than drinking frequency for the risk associated with alcohol drinking.

**DISCUSSION**

In this prospective cohort study, we found that a high alcohol intake was associated with increased risk of pancreatitis. Drinking frequency appeared to be unassociated with the risk of pancreatitis. Further, our results indicate that gallstones slightly temper the association between alcohol and pancreatitis.

**Table 3. Risk of Total Pancreatitis According to Updated Consumption of Individual Alcoholic Beverages, Copenhagen, Denmark, 1976–2007**

<table>
<thead>
<tr>
<th>Beverage Type</th>
<th>No. of Cases</th>
<th>Hazard Ratio $a$</th>
<th>95% Confidence Interval</th>
<th>Hazard Ratio $a$</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer, drinks/week</td>
<td>0</td>
<td>87</td>
<td>1.0 Referent</td>
<td>1.0 Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–6</td>
<td>74</td>
<td>1.3 0.9, 1.8</td>
<td>1.3 0.9, 1.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–13</td>
<td>25</td>
<td>1.3 0.8, 2.2</td>
<td>1.2 0.7, 2.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\geq 14$</td>
<td>49</td>
<td>2.5 1.6, 3.8</td>
<td>2.0 1.3, 3.1</td>
<td></td>
</tr>
<tr>
<td>Wine, drinks/week</td>
<td>0</td>
<td>117</td>
<td>1.0 Referent</td>
<td>1.0 Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–6</td>
<td>99</td>
<td>1.0 0.7, 1.4</td>
<td>1.1 0.8, 1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–13</td>
<td>11</td>
<td>0.7 0.4, 1.3</td>
<td>0.8 0.4, 1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\geq 14$</td>
<td>8</td>
<td>0.8 0.4, 1.7</td>
<td>0.9 0.4, 1.8</td>
<td></td>
</tr>
<tr>
<td>Spirits, drinks/week</td>
<td>0</td>
<td>145</td>
<td>1.0 Referent</td>
<td>1.0 Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–6</td>
<td>66</td>
<td>0.8 0.6, 1.1</td>
<td>0.7 0.5, 1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–13</td>
<td>16</td>
<td>1.1 0.6, 1.8</td>
<td>1.0 0.6, 1.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\geq 14$</td>
<td>8</td>
<td>1.0 0.5, 2.0</td>
<td>0.9 0.4, 1.8</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Adjusted for age, sex, and other beverage types.

$^b$ Adjusted for age, sex, smoking, education, body mass index, and other beverage types.
found in wine. However, the validity of these results is severely limited by the small number of cases in the high categories of wine and spirits and by the fact that wine drinking is associated with a generally healthier lifestyle (14).

Results on drinking frequency are limited by the fact that our measure of this drinking variable may be too crude to pick up small effects. Unfortunately, information on binge drinking (i.e., drinking a minimum number of drinks per occasion) was not available, and we cannot comment on this aspect with the present data.

Our data did not suggest a clear threshold effect of alcohol intake on the risk of pancreatitis. However, this might be due to misclassification. In the case of underreporting, the risk in the reference category would increase, and this could lead to a true threshold amount being either lowered or blurred.

Strengths include the large study size, the prospective design, and the fact that we had complete follow-up information on all 17,905 participants. In addition, to the best of our knowledge, this is the first study to investigate the association between alcohol intake and pancreatitis prospectively, even though it is considered well known that alcohol is a strong risk factor for pancreatitis.

Our findings are consistent with previous results from case-control studies (1–4), although the literature on alcohol and pancreatitis is sparse, and only one previous case-control study has included women (2). In that study, the risk of pancreatitis was not associated with alcohol among women; however, results were limited by the few female cases.

Different mechanisms have been suggested to explain the toxic effect of alcohol. The pancreas can degrade alcohol by both oxidative and nonoxidative metabolism—mechanisms involving the synthesis of acetaldehyde and fatty-acid ethanol esters, respectively (15). The latter (i.e., fatty-acid ethanol esters) have been demonstrated to cause pancreatic edema, intracellular trypsin activation, and the induction of proinflammatory transcription factors in animal studies (16–18). In addition, the toxic effect of alcohol may be due to the induction of oxidative stress, that is, the imbalance between formation and neutralization of reactive oxygen species (19–21). On the other hand, there is some evidence that a moderate alcohol intake protects against gallstone disease (7, 8), which would lower the risk of pancreatitis. This is in accordance with our finding that the risk of pancreatitis according to alcohol was increased when including gallstones in the model.

In summary, we found that a high alcohol intake was associated with an increased risk of pancreatitis in both men and women, whereas drinking frequency did not seem to be a risk factor for pancreatitis when the amount of alcohol intake was taken into consideration.

The study is supported by grants from the Danish National Board of Health and the Danish Medical Research Council.

Conflict of interest: none declared.

REFERENCES


Smoking and Risk of Acute and Chronic Pancreatitis Among Women and Men

A Population-Based Cohort Study

Janne Schurmann Tolstrup, MSc, PhD; Louise Kristiansen, BSc; Ulrik Becker, MD, DrMedSci; Morten Grønbæk, MD, PhD, DrMedSci

Background: Alcohol and gallstone disease are the most established risk factors for pancreatitis. Smoking is rarely considered to be a cause despite the fact that a few studies have indicated the opposite. We aimed to assess the independent effects of smoking on the risk of pancreatitis.

Methods: We used data from an observational, population-based cohort study conducted in Denmark. Participants were 9573 women and 8332 men who were followed up for a mean of 20.2 years. Participants underwent a physical examination and completed self-administered questionnaires about lifestyle habits. Information on incident cases of acute and chronic pancreatitis were obtained by record linkage with the Danish national registries.

Results: A total of 235 cases of pancreatitis occurred during follow-up. A dose-response association between smoking and risk of acute and chronic pancreatitis was observed in both men and women. For example, the hazard ratio of developing pancreatitis was 2.6 (95% confidence interval [CI], 1.5-4.7) among women and 2.6 (95% CI, 1.1-6.2) among men who smoked 15 to 24 grams of tobacco per day. Alcohol intake was associated with an increased risk of pancreatitis (hazard ratio, 1.09; 95% CI, 1.04-1.14 for each additional drink per day). The risk of pancreatitis associated with smoking, however, was independent of alcohol and gallstone disease. Approximately 46% of cases of pancreatitis were attributable to smoking in this cohort.

Conclusion: In this population of Danish men and women, smoking was independently associated with increased risk of pancreatitis.

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The incidence of pancreatitis has increased in recent decades.1-8 Pancreatitis can be divided into acute and chronic pancreatitis; however, disagreement exists on whether 2 distinct conditions really exist or whether acute pancreatitis leads to chronic pancreatitis.9,10 The most common symptom of both is severe abdominal pain. The mortality rate of acute pancreatitis is especially high and has not decreased since the 1970s, which is most likely because treatment has not improved and is mainly directed toward pain control.

Gallstone disease and excessive alcohol use are described as being the most common causes of acute and chronic pancreatitis, respectively. In the medical literature, smoking is generally not considered to be an important risk factor for pancreatitis, even though some case-control studies conducted in men, as well as a recent cohort study, suggest the opposite.11-18 Also, evidence from experimental studies19-22 suggests that smoking is associated with pancreas damage. In most populations, smoking is strongly associated with drinking alcohol; hence, an independent effect of smoking can be difficult to assess, especially from a case-control design because individuals with moderate to heavy alcohol intake are dominant.

Smoking may also be associated with risk of gallstone disease.23-24 If so, observed associations between smoking and pancreatitis could be explained by an increased risk of gallstones in individuals who smoke, which in turn renders these individuals at high risk of pancreatitis.

In this study, we examined the association between smoking and risk of acute and chronic pancreatitis in a large prospective cohort consisting of men and women from the general population. Our objective was to determine if smoking is associated with an increased risk of acute and chronic pancreatitis independently of alcohol use and gallstone disease.
STUDY POPULATION

Data used in this study came from the first 3 examinations of the Copenhagen City Heart Study (CCHS), performed in 1976-1978, 1981-1983, and 1991-1994. The CCHS is a prospective cohort study. The participants were randomly chosen from the general population of Copenhagen and included 14,233 men and women 20 to 95 years old in 1976-1978 (response rate, 74%). In 1981-1983, all previously invited individuals plus 500 new individuals aged 20 to 24 years were invited to participate, resulting in 12,698 participants (response rate, 70%). In 1991-1994, all previously invited individuals plus 3000 new individuals aged 20 to 49 years were invited to participate, and 10,135 of these participated (response rate, 61%). In total, 18,035 individuals participated in 1 or more examinations of the CCHS.

Before visiting the study clinic, participants completed a self-administered questionnaire (including questions on alcohol intake, smoking, physical activity, education level, and income). At the clinic visit, physical examinations were performed (including measurement of height, weight, forced expiratory volume in 1 second [FEV1], and carbon dioxide in expired air) and questionnaires were checked for missing information.

SMOKING

At each examination, participants were asked whether they smoked or had been smoking previously and, if the response was affirmative, about duration of smoking (in years). Current smokers were further asked about the usual amount of tobacco in categories of daily cigarettes, cheroots, cigars, and pipes. Assuming 1 cigarette to be equivalent to 1 g of tobacco, 1 cheroot or 1 pipe to 3 g of tobacco, and 1 cigar to 5 g of tobacco, participants were categorized in 5 groups (never-smokers, ex-smokers, and smokers of 1-14, 15-24, and ≥ 24 g/d of tobacco). Pack-years of smoking were calculated as (years of smoking × daily grams of tobacco)/20. For current smokers, duration of smoking was updated every 5 years until the participant reported having quit or was censored. For ex-smokers, we had information only on duration of smoking; therefore, pack-years could not be calculated.

COVARIABLES

For the purpose of this study, sex, smoking, education level, income, body mass index (BMI), and physical activity were considered potential confounders. Education level was categorized as less than 8 years, 8 to 11 years, and more than 11 years of education corresponding to lower primary school, higher primary school, and secondary school, respectively. Income was categorized as less than 20, 20 through 24.9, and 25 or greater. Physical activity was categorized as sedentary (light physical activity for < 2 hours per week), light (light physical activity for 2-4 hours per week), moderate (light physical activity for ≥ 4 hours per week or strenuous activity for 2-4 hours per week), and heavy (strenuous physical activity at least 4 hours per week). Concerning alcohol intake, participants were asked how often they drank beer, wine, and spirits in categories of “never/hardly ever,” “monthly,” “weekly,” and “daily” and how many drinks they drank of each type of beverage per week. The 3 types of alcoholic beverage were added up to a measure of total alcohol intake.

INFORMATION ON PANCREATITIS AND GALLSTONE DISEASE

Information on pancreatitis was obtained from the Danish Hospital Discharge Register28 and the Danish Registers of Causes of Death,29 which contain data on all hospital admissions and causes of death in Denmark, respectively. Information on incident cases of pancreatitis among the study participants in these registries was identified through linkage by the unique identification number, which is allocated to every Danish inhabitant by the Central Population Registry. The exact diagnosis for pancreatitis has not been validated, but the validity of the Danish Hospital Discharge Register is generally considered to be high.27 For acute pancreatitis, the relevant International Classification of Diseases, Eighth Revision (ICD-8) codes were 577.00, 577.01, 577.02, 577.03, 577.04, 577.08, and 577.09, along with International Statistical Classification of Diseases, 10th Revision (ICD-10) codes K85.9. For chronic pancreatitis, the relevant ICD-8 codes were 577.19, 577.90, 577.91, and 577.92, and the ICD-10 codes were K86.0, K86.1, K86.2, K86.3, and K86.9. Lastly, information on gallstone disease was also obtained from the Danish Hospital Discharge Register (ICD-8 and ICD-10 code K80).

STATISTICAL ANALYSIS

Participants accrued person-time from the time of their first participation in the CCHS until the time of their first admission to a hospital because of pancreatitis, date of death, emigration, or end of follow-up (July 9, 2007), whichever occurred first. We had follow-up information on 100% of the study participants. Analyses were performed for acute and chronic pancreatitis separately and combined (total pancreatitis). For the analysis of acute pancreatitis, participants who had a previous diagnosis of chronic pancreatitis were censored at the time of the chronic pancreatitis (n=11). Participants with missing information on smoking, alcohol intake, BMI, or school education level (n=125) or with a diagnosis of pancreatitis before baseline (n=3) were excluded from the study, which left 17,905 eligible for analysis. Data were analyzed by means of the Cox proportional hazards regression model, with delayed entry implemented (using the SAS program software, version 9.1; SAS Institute Inc, Cary, North Carolina). To ensure maximal adjustment for confounding by age, age (in days) was used as the underlying time axis. The Cox proportional hazards assumption was examined graphically and statistically by introducing interaction terms between time and alcohol consumption in the model; no violations against the assumptions were detected.

Primary analyses were performed using updated measures of alcohol consumption and other covariates, in which we prospectively assessed the risk of pancreatitis in between-examination increments, based on information on alcohol consumption and other covariates derived from the preceding questionnaire. Also, analyses were performed including only information on smoking and covariates from the first examination in which every participant had joined.

We estimated the population-attributable risk related to smoking categories (never-smoker, ex-smoker, and current smokers of 1-14, 15-24, and ≥ 25 g/d of tobacco) as $$\Sigma \text{Pe} \cdot (\text{RR} - 1)/\text{RR}$$, where Pe is the prevalence of the i'th smoking category and RR is the relative risk associated with this category.30 Interaction between alcohol intake and smoking was determined with the use of a nested log-likelihood test, comparing a model containing the variables as single terms with a model also including the interaction terms. For this particular purpose, alcohol was categorized into 3 groups (<7, 7-20, and >20 drinks per week) and smoking was categorized into 2 groups.

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(never-smokers and ex-smokers and current smokers) to increase the statistical power of the test.

**RESULTS**

**BASELINE CHARACTERISTICS**

**Table 1** gives the characteristics of 17,905 men and women categorized by smoking status as reported at the time of their first participation in the CCHS (1976-1978, 1981-1983, or 1991-1994). Overall, 58% of the women and 68% of the men were current smokers, 15% of the women and 19% of the men were ex-smokers, and 28% of the women and 13% of the men had never smoked. As expected, lung function as measured by FEV1 (in percentage of the expected value) was highest in participants who never smoked and was lowest in participants who were current smokers. Also, carbon dioxide in expired air was similar in never-smokers and ex-smokers and increased with increasing amounts of tobacco used per day. On average, current smokers drank more alcohol and were less physically active compared with never-smokers.

**SMOKING STATUS, PACK-YEARS, AND RISK OF PANCREATITIS**

The mean follow-up in this study was 20.2 years (range, 0-28.3 years). At the end of follow-up, a total of 235 participants (113 women and 122 men) had developed pancreatitis, and there were 160 cases of acute and 97 cases of chronic pancreatitis (the number of cases of acute and chronic pancreatitis does not equal the total number of cases because some people had both acute and chronic pancreatitis and they were only counted once in the total number of cases).

We performed analyses by modeling the risk of acute and chronic pancreatitis combined (total pancreatitis) according to categories of smoking status (Table 2). Similar risk estimates were observed in women and men: for example, the hazard ratio of developing pancreatitis was 2.6 (95% confidence interval [CI], 1.5-4.7) among women and 2.6 (95% CI, 1.1-6.2) among men who smoked 15 to 24 grams per day of tobacco. Combining women and men (P value for interaction between sex and smoking status in nested log likelihood test was .70) in an analysis adjusted for age and sex and in an analysis further adjusted for alcohol, education level, and BMI, current smokers had a higher risk of both acute and chronic pancreatitis compared with never-smokers, and risk estimates were similar for the 2 outcomes (Table 3). For ex-smokers, however, the hazard ratio for acute pancreatitis was 2.3 (95% CI, 1.3-4.1), whereas the hazard ratio for chronic pancreatitis was 0.9 (95% CI, 0.4-2.0). For total pancreatitis, adjusted hazard ratios were 1.7 (95% CI, 1.0-2.7), 1.5 (95% CI, 0.9-2.5), 2.5 (95% CI, 1.5-3.9), and 3.3 (95% CI, 1.9-5.8) among ex-smokers and current smokers of 1 to 14, 15 to 24, and 25 g/d or more of tobacco, respectively. In the multivariable-adjusted models, alcohol was responsible for most of the effect of adjustment. The adjusted hazard ratio for amount of alcohol intake was 1.09.
(96% CI, 1.04-1.14) for each additional drink per day. The inclusion of variables for personal income and physical activity to the fully adjusted model had negligible effect on the size and precision of the risk estimates. The fully adjusted risk of pancreatitis in women compared with men was 0.9 (95% CI, 0.6-1.1). Repeating the analyses without updating information on smoking and other variables did not change our results (data not shown).

To explore if the relatively high risk among ex-smokers was due to sick-quitters (ie, participants who have given up smoking because of early symptoms of pancreatitis), we performed additional analyses omitting the first 2 variables for follow-up and updating smoking variables and covariables with a delay of 2 years. However, this only affected risk estimates slightly. Compared with the hazard ratio estimated for the entire follow-up period (1.7; 95% CI, 1.0-2.7), the hazard ratio was 1.6 (95% CI, 1.0-2.6) when omitting the first 2 years of follow-up.

Hazard ratios of acute, chronic, and total pancreatitis according to pack-years of smoking for current smokers and smoking duration for ex-smokers are given in Table 4. Dose-response associations were observed and again the associations for risk of acute and chronic pancreatitis were similar. For example, hazard ratios of acute and chronic pancreatitis were 3.2 (95% CI, 1.6-6.2) and 3.1 (95% CI, 1.3-7.1) among participants who had smoked 45 to 59 pack-years compared with never-smokers. Assuming that the multivariable-adjusted hazard ratios represent biologically causal associations between smoking status and risk of pancreatitis, we estimated that approximately 46% of cases of pancreatitis were attributable to smoking in this cohort.

We repeated the analyses stratifying by amount of alcohol intake: participants who in each examination reported drinking maximally 2 drinks per day for women and 3 drinks per day for men were categorized as consistent light to moderate drinkers, and participants who in at least 1 examination reported drinking above these limits were categorized as heavy drinkers. Most of the cases occurred among the consistent light to moderate drinkers (162 of 235 cases totally). Among these, hazard ratios were 1.6 (95% CI, 0.9-2.6), 1.5 (95% CI, 0.9-2.6) for each additional drink per day. The inclusion of variables for personal income and physical activity to the fully adjusted model had negligible effect on the size and precision of the risk estimates. The fully adjusted risk of pancreatitis in women compared with men was 0.9 (95% CI, 0.6-1.1). Repeating the analyses without updating information on smoking and other variables did not change our results (data not shown).

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Hazard ratios of acute, chronic, and total pancreatitis according to pack-years of smoking for current smokers and smoking duration for ex-smokers are given in Table 3. Risk of Acute, Chronic, and Total Pancreatitis by Updated Information on Smoking Status in Men and Women Combined

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Never</th>
<th>Former</th>
<th>1-14 g/d of Tobacco</th>
<th>15-24 g/d of Tobacco</th>
<th>≥25 g/d of Tobacco</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute pancreatitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>16</td>
<td>45</td>
<td>34</td>
<td>44</td>
<td>21</td>
</tr>
<tr>
<td>Crude hazard ratio (95% CI)</td>
<td>1.0</td>
<td>2.4 (1.3-4.2)</td>
<td>1.9 (1.1-3.5)</td>
<td>2.8 (1.6-5.1)</td>
<td>4.3 (2.2-8.5)</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)b</td>
<td>1.0</td>
<td>2.3 (1.3-4.1)</td>
<td>2.0 (1.1-3.6)</td>
<td>2.8 (1.5-5.0)</td>
<td>3.8 (1.9-7.5)</td>
</tr>
<tr>
<td><strong>Chronic pancreatitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>11</td>
<td>13</td>
<td>18</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td>Crude hazard ratio (95% CI)</td>
<td>1.0</td>
<td>0.9 (0.4-2.0)</td>
<td>1.3 (0.6-2.7)</td>
<td>2.4 (1.2-4.9)</td>
<td>4.2 (1.9-9.0)</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)b</td>
<td>1.0</td>
<td>0.9 (0.4-2.0)</td>
<td>1.1 (0.5-2.3)</td>
<td>2.0 (1.0-4.1)</td>
<td>3.3 (1.5-7.3)</td>
</tr>
<tr>
<td><strong>Total pancreatitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>26</td>
<td>54</td>
<td>48</td>
<td>72</td>
<td>35</td>
</tr>
<tr>
<td>Crude hazard ratio (95% CI)</td>
<td>1.0</td>
<td>1.7 (1.0-2.7)</td>
<td>1.6 (1.0-2.6)</td>
<td>2.6 (1.7-4.1)</td>
<td>3.9 (2.3-6.7)</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)b</td>
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<td>2.5 (1.5-3.9)</td>
<td>3.3 (1.9-5.8)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

Results from Cox proportional hazards regression analysis with age as the underlying time scale.

bAdjusted for sex, education level (<8 years, 8-11 years, >11 years), body mass index (calculated as weight in kilograms divided by height in meters squared; <20, 20-24.9, ≥25), and alcohol intake (continuous).
2.4), 2.3 (95% CI, 1.4-3.8), and 2.9 (95% CI, 1.5-5.8) in ex-smokers and current smokers of 1 to 14, 15 to 24, and 25 g/d or more of tobacco, respectively. Corresponding hazard ratios among the heavy drinkers were 1.7 (95% CI, 0.5-5.2), 1.4 (95% CI, 0.5-4.6), 2.4 (95% CI, 0.8-6.8), and 3.3 (95% CI, 1.1-10).

Incidence rates for total pancreatitis by smoking and alcohol are shown in the Figure. Within each category of alcohol intake, the incidence rate was higher among ex-smokers and current smokers compared with never-smokers. We found no evidence of interaction between alcohol intake and smoking on the risk of pancreatitis ($P = .70$).

**GALLSTONES AS A POTENTIAL MEDIATOR OF THE ASSOCIATION BETWEEN SMOKING AND PANCREATITIS**

We performed analyses of gallstones as a potential mediator of the association between smoking and risk of pancreatitis. In total, 562 women and 251 men had gallstones before the end of follow-up. As expected, gallstones were associated with subsequent risk of pancreatitis (adjusted hazard ratio for total pancreatitis, 11; 95% CI, 7.7-15). However, adjusting for gallstones had little influence on our results, indicating that gallstone disease does not mediate the association between smoking and pancreatitis. For example, the adjusted hazard ratio of total pancreatitis among participants who smoked 15 to 24 g/d of tobacco was 2.5 (95% CI, 1.5-3.9) (Table 3) and 2.3 (95% CI, 1.5-3.7) after further adjustment for gallstones. In separate analyses of acute and chronic pancreatitis, including gallstones in the model did not affect our results.

To see if smoking is associated with increased risk of gallstone-associated pancreatitis, we performed exploratory analyses restricted to participants who had gallstones before or concomitant with pancreatitis diagnosis. This accounted for 831 participants of whom 65 developed pancreatitis during follow-up. In this subgroup, the adjusted hazard ratio of total pancreatitis was 1.4 (95% CI, 0.7-2.7) among ex-smokers and smokers of 1 to 14 g/d of tobacco combined and was 0.9 (95% CI, 0.4-2.1) among smokers of 15 g/d of tobacco or more. Lastly, analyses were performed on participants free of gallstone disease and who were consistent light to moderate drinkers (idiopathic pancreatitis). In this subgroup, results were similar to main results.

**COMMENT**

In this large population-based study with long follow-up, we found that participants who at baseline reported smoking or being previous smokers had higher risks of developing acute and chronic pancreatitis compared with nonsmokers. We found comparable effect sizes in women and men and for acute and chronic pancreatitis. Furthermore, results strongly indicate that associations are independent of alcohol intake and of gallstone disease, which are risk factors considered to account for most cases of pancreatitis.
Most previous studies on smoking and pancreatitis find
an increased risk among smokers; however, 2 case-
control studies11,12 did not observe an increased risk, but
these studies included only individuals with alcohol use
disorders (ie, persons with a heavy alcohol intake and
thus a high risk of pancreatitis). Hence, relative risk es-
timates of pancreatitis according to smoking may be
smaller than for individuals with a lower alcohol intake.
Only 2 of the 4 studies12,18 in which women are in-
cluded found an increased risk of pancreatitis according
to smoking in women, and 1 of these studies12 found only
a weak association. In the present study, we observed simi-
lar risks in men and women. Recently, Lindkvist et al11
found an increased relative risk of 2.14 for developing
acute pancreatitis in current smokers in a prospective
cohort study. In that study, a dose-response effect was
also observed after controlling for alcohol intake,
whereas no adjustment for gallstone disease was per-
formed. We did not observe an increased risk of pancre-
atitis according to smoking among participants with
preceding or concomitant gallstone disease. This find-
ing is in accordance with results of a study18 that found
that smoking was only associated with alcohol-associated
and idiopathic pancreatitis, which also agrees with our
findings.

The risk of total pancreatitis in ex-smokers was of simi-
lar size to the risk among light current smokers (1-14 g/d
of tobacco). This relatively high risk in the ex-smokers
did not seem to be attributable to sick-quitters because
omitting 2 and 4 years of follow-up, respectively, had only
limited effect on the size of the hazard ratio. Lung func-
tion (as measured by FEV1) within smoking categories
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ranged in the expected order (decreasing in the order of
never-smokers, ex-smokers, and current smokers of 1-14,
15-24, and >25 g/d of tobacco, respectively). This find-
ing further indicates that there was not a high propor-
tion of sick-quitters among the ex-smokers. Also, the
amount of carbon dioxide in expired air was similar among
never-smokers and ex-smokers, which indicates that there
was not a substantial fraction of current smokers who
were misclassified as ex-smokers.

A high proportion of participants were smokers in this
study cohort. A total of 62% were current smokers at their
first enrollment in the CCHS, and we found that approxi-
mately 46% of the cases of pancreatitis in this cohort could
be attributed to smoking. Currently, the proportion of
smokers in the Danish population, as in most Western
populations, has decreased to approximately 30%, and
never-smokers and ex-smokers account for approximately 39% and 31%, respectively.33

This study has the advantages of a prospective de-
sign, large size, and complete follow-up information on
all participants. A limitation of the study is that the di-
agnoses of acute and chronic pancreatitis in the Danish
Hospital Discharge Register have not been validated. Only
hospital admissions are registered, and contacts to gen-
eral practitioners are not included. Hence, it is likely that
not all cases of pancreatitis occurring during the study
period are categorized as such in this study. Also, some
misclassification between the diagnoses of acute and
chronic pancreatitis have probably occurred because the
symptoms and diagnostic criteria of acute and chronic
pancreatitis are overlapping and the 2 diseases can co-
exist.34 Such misclassification would result in similar ob-
served associations between smoking and risk of acute
and chronic pancreatitis, whereas the results for the joint
outcome of pancreatitis are valid. Furthermore, we did
not have information on the cause of the pancreatitis, and
risk factors for gallstone-related pancreatitis may not be
the same as for alcohol-related or idiopathic pancreati-
tis.11,18 We addressed this issue in exploratory analyses,
defining gallstone-related pancreatitis as cases of pan-
creatitis with preceding or concomitant gallstone dis-
estease and idiopathic pancreatitis as cases of pancreatitis
with no history of gallstone disease and heavy alcohol
intake. We also observed in accordance with previous
studies19 that smoking does not seem to be associated with
increased risk of gallstone-related pancreatitis.

We observed an 11-fold risk of pancreatitis among par-
ticipants with gallstone disease. However, this result
should be interpreted with caution because almost all pa-
ients with pancreatitis are examined by abdominal ul-
trasoundography at hospitalization, and gallstones will be
detected also in patients with pancreatitis of other causes
with prevalent gallstones unrelated to the attack of pan-
creatitis. Hence, a part of the rather large relative risk of
pancreatitis according to gallstones may be owing to de-
tection bias.

Apart from the epidemiologic evidence of an associa-
tion between smoking and development of acute and
chronic pancreatitis, a biological effect of smoking seems
plausible because both animal studies and human studies19,21,35,36 have demonstrated changes of the pancreas and
in pancreatic functioning after exposure to tobacco smoke.

In conclusion, we found that smoking was associ-
at with an increased risk of acute and chronic pancre-
atitis in both men and women. The risk associated with
smoking was independent of alcohol and gallstone dis-
ease, which are risk factors suggested to be the main causes
of pancreatitis.

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tansen, and Becker. Drafting of the manuscript: Tolstrup.
Critical revision of the manuscript for important intel-
lectual content: Tolstrup, Kristiansen, Becker, and Gron-
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