Incidence of Cardiovascular and Cerebrovascular Disease in Danish Men and Women With a Prolonged Heavy Alcohol Intake

Ulla Arthur Hvidtfeldt, Marie Engholm Frederiksen, Lau Caspar Thygesen, Mads Kamper-Jørgensen, Ulrik Becker, and Morten Grønbæk

Background: Several epidemiological studies have found U- or J-shaped relationships between alcohol intake and cardiovascular conditions. The influence of heavy drinking is, however, sparsely studied. The objective of the present study was to examine whether alcohol addicts have higher incidence rates of cardio- and cerebrovascular diseases than the population in general.

Methods: The cohort comprised 19,185 subjects (15,368 men and 3,817 women) who attended outpatient clinics for alcohol abusers within the Copenhagen Hospital Corporation (1954 to 1992). Incidence rates were standardized (SIR) according to sex, age and calendar time to compare subjects’ cardio- and cerebrovascular incidence with that of the general population of Copenhagen.

Results: During the period 1977 to 2001 a total of 9,397 events of cardio- and cerebrovascular disease were observed. In both men and women, statistically significant higher incidence rates than would be expected in a standard population were observed for cardiovascular diseases (e.g., ischemic heart diseases, men: SIR = 1.76; 95% CI 1.69–1.83; women: SIR = 2.44; 95% CI 2.19–2.73) and cerebrovascular diseases (e.g., hemorrhagic stroke, men: SIR = 2.71; 95% CI 2.45–2.99; women: SIR = 2.77; 95% CI 2.18–3.48).

Conclusions: The study indicates increased risks of cardio- and cerebrovascular diseases in subjects with an excessive alcohol intake.

Key Words: Alcohol, Cardiovascular Diseases, Cerebrovascular Diseases, Incidence.

A VAST NUMBER of epidemiological studies among subsets of normal, light- to moderately drinking populations have found the relationship between alcohol and cardio- and cerebrovascular disease to be U- or J-shaped, i.e., a moderate intake of alcohol appears to be protective of cardio- and cerebrovascular disease compared to abstinence and heavy drinking (Camacho et al., 1987; Colditz et al., 1985; Gronbaek et al., 2000; Mukamal et al., 2003; Reynolds et al., 2003; Rimm et al., 1991; Thun et al., 1997; Truelsen et al., 1998; Wannamethee and Shaper, 1996). This protective effect of alcohol has especially been observed for ischemic heart disease, where the lowest risk is seen at an intake of 1 to 2 drinks per day (Klatsky, 1994; Klatsky et al., 1990; McElduff and Dobson, 1997; Rimm et al., 1991). However, the influence of heavy drinking on cardiovascular conditions is sparsely studied (Nicholls et al., 1974; Pell and D’Alonzo, 1973; Robinette et al., 1979). Often large population studies include only a small percentage of heavy drinking subjects resulting in limited power to study the health effects of heavy drinking (Rimm et al., 1991). Also, cohorts comprising heavy drinkers may be biased towards the inclusion of heavy drinkers who tolerate alcohol well or who have a relatively more favorable drinking pattern or lifestyle.

Studies within this field of research are often limited by the lack of differentiation between various cardiovascular conditions, though some have found the association between alcohol and different cardio- and cerebrovascular diseases to be disparate. For instance, while alcohol appears to protect against atherosclerosis (Iso et al., 2004; Klatsky, 1994; Klatsky et al., 1990, 2002; Reynolds et al., 2003; Stampfer et al., 1988), adverse effects have been documented in hypertension (Beilin and Puddey, 2006; Corrao et al., 1999; Klatsky et al., 1990; MacMahon, 1987), hemorrhagic stroke (Corrao et al., 1999; Klatsky, 1994; Klatsky et al., 1990, 2002; Reynolds et al., 2003; Stampfer et al., 1988), and cardiomyopathy (Gavazzi et al., 2000; Komajda et al., 1986; Lazarevic et al., 2000). Cardiomyopathy in particular has been suspected of being associated with a heavy prolonged alcohol intake, and several clinical studies have indicated a causal relationship (Gavazzi et al., 2000; Komajda et al., 1986; Lazarevic et al.,...
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2000). Consequently, it may be advantageous to analyse the different subgroups of cardio- and cerebrovascular conditions separately (Klatsky, 1994).

The objective of the present study was to examine whether excessive alcohol intake is associated with higher cardio- and cerebrovascular incidence rates compared to the general population.

MATERIALS AND METHODS

The present study was based on Danish data from The Copenhagen Alcohol Cohort comprising patients who have attended Copenhagen outpatient clinics for alcoholics. This alcohol unit consists of 5 outpatient clinics located on each of the somatic hospitals within the Copenhagen hospital Corporation. Since 1954, all patients have been registered consecutively. Through interviews with the trained staff of nurses and social workers, information on sex, age, date of birth as well as social and alcohol related issues were obtained for each subject at first contact with the outpatient clinic. Information on average number of drinks per day and duration of alcohol misuse was recorded in medical records independently of the interview, but at the same time as the interview was carried out. By review of these medical records data on average number of drinks per day and duration of alcohol misuse was attached to the rest of the dataset.

In total, the cohort comprises 15,368 men and 3,817 women between the age of 14 and 83 years at time of first admission (mean age was 38.2 years in men and 38.7 years in women). The structured registration of patients was changed in 1992, which is why patients registered after this time were not included in the present analysis.

The Danish Civil Registration System was established in 1968, ensuring that all live-born infants as well as current and new residents are assigned a unique Personal Identification Number (PIN). Using the PIN the cohort data were linked with the Danish National Patient Registry, which contains information on all somatic hospital admissions since 1st of January 1977. For each admission a discharge diagnosis classified according to the International Classification of Diseases is recorded. In the period from 1977 to 1993 diagnoses were classified according to the eighth revision, and from 1994 onwards diagnoses were classified according to the 10th revision. Cohort data were furthermore linked with the Central Danish Death Register. In this way complete follow-up on the health status of the subjects was ensured and we were able to identify subjects’ cardio- and cerebrovascular hospitalizations and deaths from 1977 to 2001.

In the present study, we excluded subjects who died before 1977 (n = 1,458), and subjects who had been admitted to the hospital due to a cardio- or cerebrovascular disease prior to their first attendance at the outpatient clinic. However, this was only possible in subjects entering the cohort after 1st of January 1977, as information before this period was not available.

The primary end point of the present study was cardio- and cerebrovascular morbidity and mortality. We grouped the various cardio- and cerebrovascular conditions into the following groups: Ischemic heart diseases (ICD-8 codes 410-14 and ICD-10 codes I20-I25), acute myocardial infarction (AMI) (ICD-8, 410; ICD-10, 121-22), other heart diseases (ICD-8, 420-29; ICD-10, I30-I52), cerebrovascular diseases (ICD-8, 430-38; ICD-10, I60-I67 and 169), ischemic stroke (ICD-8, 433; ICD-10, I63), haemorrhagic stroke (ICD-8, 430-31; ICD-10, I60-I62), arterial, arteriolar and capillary diseases (ICD-8, 440-8; ICD-10, I70-9), atherosclerosis and aortic and arterial aneurysms (ICD-8, 440-42; ICD-10, I70-72), and cardiomyopathy (ICD-8, 425; ICD-10, I42-I43).

The outcome variable of the present study was based on either the first cardio- or cerebrovascular hospital admission or a cardio- or cerebrovascular death diagnosis. The death diagnosis was merely considered if the subject had not previously been admitted to the hospital with the respective cardio- or cerebrovascular diagnosis.

Subjects who died on the same day as their first cardio- or cerebrovascular hospital admission were coded based on their admission diagnosis, irrespective of whether they died of the same or a different cardio- or cerebrovascular condition.

We coded the cardio- and cerebrovascular hospital admissions and deaths in the following manner: Subjects admitted with one or more of the above mentioned diagnoses were coded in accordance with the main group (e.g., ischemic heart diseases). Subjects diagnosed with one of the above mentioned specific diseases were coded according to this group as well (e.g., acute myocardial infarction). If a subject had more than one of the relevant diagnoses, he or she was coded as belonging to these corresponding main groups.

The data were analysed by standardized incidence ratios (SIR), comparing the observed number of cases in the cohort with an expected number obtained from incidences in the general population (Breslow and Day, 1987). This method allowed us to examine to which degree the incidence of cardio- and cerebrovascular disease in the cohort differed from that of the general population. The cohort was compared to the citizens of the County of Copenhagen and Municipalities of Copenhagen and Frederiksberg. This was preferred over a comparison with the general population of Denmark, as the study population merely comprised citizens of Copenhagen, and the life expectancy, and hence the health status, in Copenhagen is lower than that of the general Danish population (Juel, 2004).

We calculated person-years at risk for each subject from the date of entering the outpatient clinic, or from the 1st of January 1977 (if the subject’s entry date was before this date), until time of cardio- or cerebrovascular hospital admission, immigration, date of death, or until the end of the study period (31st of December 2001), whichever occurred first.

Expected numbers of cardio- and cerebrovascular cases were derived by multiplying age- (5-year groups) and sex-specific incident rates with the number of person-years at risk. These were summarized in order to obtain the overall expected numbers of cases indirectly standardized for age and time trends.

The SIR was estimated as the ratio of the observed number of cases to the expected number. In addition, tests of significance and 95% confidence intervals were calculated according to formulas given by Breslow & Day assuming that the observed numbers followed a Poisson distribution (Breslow and Day, 1987).

RESULTS

Baseline characteristics are given in Table 1. More than 90% of the patients fulfilled the ICD-10 criteria for alcohol addiction. Average alcohol intake in men was 21.8 drinks per day, ranging from 0 to 95 (median = 20.0) while women had

<table>
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<tr>
<th>Table 1. Characteristics of the Study Population and the General Danish Population</th>
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<tbody>
<tr>
<td>Danish population</td>
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<tr>
<td>Copenhagen alcohol cohort</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Alcohol intake, drinks/day</td>
</tr>
<tr>
<td>Duration of abuse, years</td>
</tr>
<tr>
<td>Mean age at entry, years</td>
</tr>
<tr>
<td>Married, %</td>
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<tr>
<td>Educated, %</td>
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<tr>
<td>Working, %</td>
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</tbody>
</table>

*Based on sales statistics.*
an average alcohol intake of 16.5 drinks per day, ranging from 1 to 72 (median = 15.0). In comparison, the general Danish adult population consumes on average 11.5 l of pure alcohol per year; corresponding to an average daily alcohol intake of 2.2 drinks per day. The average duration of abuse at entry to the outpatient clinic was 13.8 years in men and 8.8 years in women and 77% of the men and 74% of the women were drinking daily as opposed to periodic consumption. The percentage of working subjects was considerably lower in the cohort compared to the general Danish population since only 26.7% of the men (vs. 69.2% in the general population) and 22.4% of the women (vs. 58.4%) were working. The proportion of the cohort without education was 48% in men and 56% in women, while this percentage in the general Danish population is 25 and 32, respectively. In addition, the percentage of married subjects was also considerably lower in the cohort compared to the Danish population in both men (22% vs. 52%) and women (23% vs. 50%) (Kjoeller and Rasmussen, 2002) (Table 1).

The calculated SIRs and 95% confidence intervals for both men and women are shown in Table 2. During the period 1st of January 1977 to 31st of December 2001, a total of 7,403 events of cardiovascular diseases and 1,994 events of cerebrovascular diseases were observed in the cohort.

Statistically significant higher incidence rates than expected, were observed for all the studied main- and subgroups. In both men and women, strong excess risks were observed for cardiomyopathy, arterial, arteriolar and capillary diseases, and atherosclerosis and aneurysms. In women, this applies for ischemic heart diseases and other heart diseases as well. Moderately elevated risks are noted for acute myocardial infarction in both men and women and for ischemic heart diseases and other heart diseases in men.

In both men and women, a strong excess risk was observed in the main group of cerebrovascular diseases, as well as in the 2 subgroups ischemic stroke, and haemorrhagic stroke.

**DISCUSSION**

Findings from this study indicate that alcohol addicts are at increased risk of both cardio- and cerebrovascular diseases.

Several plausible explanations for a lowered risk of cardio- and cerebrovascular disease among moderate drinkers compared to abstainers have been discussed. The most important of these mechanisms involves an increased blood concentration of high-density lipoprotein cholesterol, decreased plasma fibrinogen levels, increased insulin sensitivity, and a reduction in platelet aggregation and thereby protection against coronary heart disease (Davies et al., 2002; Klatsky, 1994; MacMahon, 1987; Marmot and Brunner, 1991; Mukamal et al., 2005b; Renaud and de Lorgeril, 1992; Rimm et al., 1999). The apparent unfavourable effect of a heavy alcohol intake on the pathophysiology of cardio- and cerebrovascular diseases compared to a lower intake is less well described. However, it has been hypothesized, that a heavy alcohol intake could induce cardio- and cerebrovascular diseases by increasing blood pressure and triglyceride levels (Puddey and Beilin, 2006).

Previous population studies have suggested some adverse effects of heavy alcohol consumption on cardio- and cerebrovascular diseases (cf. the U- or J-shaped curve) (Camacho et al., 1987; Colditz et al., 1985; Corrao et al., 1999; Gronbaek et al., 2000; Mukamal et al., 2003; Reynolds et al., 2003; Rimm et al., 1991; Thun et al., 1997; Truelsen et al., 1998; Wannamethee and Shaper, 1996). In this regard, our results correspond with findings of previous studies. However, the risks of ischemic heart diseases and other heart diseases in men, and the risk of AMI in both men and women were only moderately elevated compared to the standard population. As subjects in the present study have been exposed to excessive alcohol consumption long before the beginning of our follow up, our findings could reflect a “healthy drinker selection,” i.e., heavy drinkers sensitive to alcohol may have become sick or died before attending the outpatient clinic and thus excluded from the present study. Consequently, the present study population may consist of particularly healthy alcoholics compared to the excluded alcoholics. However, previous studies comparing the Copenhagen Alcohol Cohort to the general population with regard to other health outcomes are not indicative of a particularly healthy cohort. One study reported a 27-fold excess mortality from alcoholic liver cirrhosis in men and a 35-fold excess mortality in women in the Copenhagen Alcohol Cohort compared to the general Danish population (Kamper-Jorgensen et al., 2004). In addition, another study reported increased risks of different types of cancer, among them pancreatic cancer (RR = 1.3; 95% confidence interval 2.19–2.73).

**Table 2.** Observed (O) and Expected (E) Number of Cases and Standardised Incidence Ratios (SIR) With 95% Confidence Intervals (CI)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>E</td>
</tr>
<tr>
<td>Ischemic heart diseases</td>
<td>2433</td>
<td>1383.5</td>
</tr>
<tr>
<td>AMI</td>
<td>1306</td>
<td>908.4</td>
</tr>
<tr>
<td>Other heart diseases</td>
<td>2017</td>
<td>1044.2</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>174</td>
<td>61.0</td>
</tr>
<tr>
<td>Arterial, arteriolar, etc.</td>
<td>1053</td>
<td>472.1</td>
</tr>
<tr>
<td>Atherosclerosis, aneurysms</td>
<td>921</td>
<td>376.5</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>1668</td>
<td>728.6</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>447</td>
<td>180.8</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>398</td>
<td>146.7</td>
</tr>
</tbody>
</table>
CI 1.0–1.8) and liver cancer (RR = 3.9; 95% CI 2.8–5.4) (Tonnesen et al., 1994). Subjects entering a treatment program at baseline increase their chance of alcohol abstinence and if a large proportion of the subjects became abstainers during follow up, the observed SIRs could be blurred, as abstinence too is considered a risk factor of cardio- and cerebrovascular diseases. In addition, a change from heavy consumption to more moderate levels could also affect the risks towards lower SIR estimates.

It is recognized that alcohol intake and smoking habits are strongly correlated (Jensen et al., 2003), and as smoking is a well-established risk factor for cardio- and cerebrovascular diseases, the results of the present study could be confounded by smoking. Information on the smoking habits of the cohort was not available. Methodological studies have concluded, however, that only substantially different distributions of smoking habits in the 2 groups of comparison would cause a considerable confounding effect (Axelson, 1989). Furthermore, a previous study investigating the incidence of cancers in the cohort found that the SIR of lung cancer was only modestly increased in this cohort compared to the general population (SIR = 2.6; 95% CI 2.3–2.8) (Tonnesen et al., 1994). This indicates that smoking to some extend may account for some of the higher incidence of cardio- and cerebrovascular diseases in this cohort.

Information on the morbidity of the subjects was obtained through linkage with the Danish National Patient Registry (LPR), which only holds information on hospitalizations. Therefore, regarding information on diseases frequently treated in primary health care, such as angina pectoris, the Register will only provide information on the most serious proportion of the disease spectrum, while diseases such as acute myocardial infarction, almost inevitably leading to hospitalization or perhaps sudden death, are more likely to be registered. As a result, underreporting of cases regarding the less serious conditions in question may have occurred. Furthermore, subjects with undiagnosed cardio- or cerebrovascular diseases must be expected to appear in the cohort, causing underreporting of morbidity. With regard to certain diseases of which alcohol is considered a risk factor, it is possible that a doctor will provide a more thorough examination, and thus detect more cases, if she is aware of the patient’s excessive alcohol abuse. This type of differential misclassification could have exaggerated the effect of alcohol on cardio- and cerebrovascular diseases.

Information on hospitalizations was only available in the Danish National Patient Registry from January 1, 1977. This hindered exclusion of subjects who had been admitted to the hospital with cardio- or cerebrovascular diseases prior to this date. This makes a causal inference questionable, as the temporal separation of cause and effect may be lacking. Additional analyses excluding the first 5 years of follow up showed similar incidence ratios (data not shown), indicating that pre-existing disease was not a crucial problem in this study.

It is important to note that the groups in question presumably differ with respect to lifestyle characteristics influencing the risk of cardio- and cerebrovascular diseases other than the amount of alcohol consumed, e.g., smoking, diet, physical activity or body mass index. Therefore, we are not able to conclude that the observed higher incidence rates of the cohort compared to the general population are caused by alcohol, i.e., a causal inference may be questionable. Finally, although the applied type of analysis accounts for age and calendar time, no element of duration of abuse before attendance at the outpatient clinic is included. In this regard, subjects are treated equally irrespective of whether they are life-long or short-term abusers. This could lead to differential misclassification if these 2 groups vary according to treatment response.

The present study was based on a large cohort of heavily drinking men and women who were followed prospectively. Both study design and the size of the study population distinguishes this study from previous studies on alcohol abusers (Nicholls et al., 1974; Pell and D’Alonzo, 1973; Robinette et al., 1979). Selection bias due to loss of follow up was not relevant in the present study because of the access to population covering register data. The considerable size of the cohort made it possible to examine effects on both men and women. Moreover, we were able to distinguish between various types of cardio- and cerebrovascular conditions.

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**CONFLICTS OF INTEREST**

None.

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**REFERENCES**


