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

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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 (\(P_{\text{trend}}<0.001\)). 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

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, % &lt;8 years</th>
<th>Mean Body Index, kg/m²</th>
<th>Physical Inactivity, %</th>
<th>Low Income, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2,953</td>
<td>Beer, wine, spirits</td>
<td>55 (33, 73)</td>
<td>Current</td>
<td>Past</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–6</td>
<td>948</td>
<td></td>
<td>54 (32, 75)</td>
<td>Current</td>
<td>Past</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7–13</td>
<td>1,856</td>
<td></td>
<td>50 (25, 71)</td>
<td>Current</td>
<td>Past</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–20</td>
<td>1,989</td>
<td></td>
<td>50 (24, 70)</td>
<td>Current</td>
<td>Past</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21–34</td>
<td>1,383</td>
<td></td>
<td>51 (26, 70)</td>
<td>Current</td>
<td>Past</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–48</td>
<td>566</td>
<td></td>
<td>51 (30, 69)</td>
<td>Current</td>
<td>Past</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;48</td>
<td>471</td>
<td></td>
<td>50 (24, 67)</td>
<td>Current</td>
<td>Past</td>
<td></td>
<td></td>
<td></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>
<thead>
<tr>
<th>Alcohol Intake, drinks/week</th>
<th>Total Pancreatitis</th>
<th>Chronic Pancreatitis</th>
<th>Acute Pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>Hazard Ratio</td>
<td>95% Confidence Interval</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>0</td>
<td>1.0</td>
<td>Referent</td>
<td>1.0</td>
</tr>
<tr>
<td>1–6</td>
<td>0.9</td>
<td>0.6, 1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>7–13</td>
<td>0.8</td>
<td>0.5, 1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>14–20</td>
<td>0.8</td>
<td>0.5, 1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>21–34</td>
<td>0.7</td>
<td>0.4, 1.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

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

*Adjusted for age and sex.

**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 1.13 (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.

Limitations include a lack of information on potential confounders, such as diet and coffee (4, 12). Furthermore, the diagnosis of pancreatitis has not been validated. In the Danish Hospital Discharge Register, only hospital admissions and not contacts with general practitioners are registered; hence, it is likely that we do not have information on all cases occurring during the study period. Moreover, misclassification between the diagnoses of acute and chronic pancreatitis has most likely occurred, as the symptoms and diagnostic criteria are overlapping and the 2 diseases can coexist (13). Such misclassification would result in similar observed associations between alcohol and risk of acute and chronic pancreatitis. Therefore, for these reasons and because of the limited number of cases, we recommend that readers do not place too much emphasis on this result. However, results for the joint outcome of pancreatitis are valid.

We found an increased risk of pancreatitis when drinking >14 drinks of beer/week, whereas no association was observed for wine or spirits. For wine, this result could hypothetically be due to a protective effect of the antioxidants

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**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</th>
<th>95% Confidence Interval</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer, drinks/week</td>
<td>0</td>
<td>1.0</td>
<td>Referent</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>1–6</td>
<td>74</td>
<td>1.3</td>
<td>0.9, 1.8</td>
<td>1.3</td>
<td>0.9, 1.8</td>
</tr>
<tr>
<td>7–13</td>
<td>25</td>
<td>1.3</td>
<td>0.8, 2.2</td>
<td>1.2</td>
<td>0.7, 2.0</td>
</tr>
<tr>
<td>≥14</td>
<td>49</td>
<td>2.5</td>
<td>1.6, 3.8</td>
<td>2.0</td>
<td>1.3, 3.1</td>
</tr>
<tr>
<td><strong>P</strong>&lt;sup&gt;trend&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wine, drinks/week</td>
<td>0</td>
<td>1.0</td>
<td>Referent</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>1–6</td>
<td>99</td>
<td>1.0</td>
<td>0.7, 1.4</td>
<td>1.1</td>
<td>0.8, 1.5</td>
</tr>
<tr>
<td>7–13</td>
<td>11</td>
<td>0.7</td>
<td>0.4, 1.3</td>
<td>0.8</td>
<td>0.4, 1.5</td>
</tr>
<tr>
<td>≥14</td>
<td>8</td>
<td>0.8</td>
<td>0.4, 1.7</td>
<td>0.9</td>
<td>0.4, 1.8</td>
</tr>
<tr>
<td><strong>P</strong>&lt;sup&gt;trend&lt;/sup&gt;</td>
<td>0.21</td>
<td>0.49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spirits, drinks/week</td>
<td>0</td>
<td>1.0</td>
<td>Referent</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>1–6</td>
<td>66</td>
<td>0.8</td>
<td>0.6, 1.1</td>
<td>0.7</td>
<td>0.5, 1.0</td>
</tr>
<tr>
<td>7–13</td>
<td>16</td>
<td>1.1</td>
<td>0.6, 1.8</td>
<td>1.0</td>
<td>0.6, 1.7</td>
</tr>
<tr>
<td>≥14</td>
<td>8</td>
<td>1.0</td>
<td>0.5, 2.0</td>
<td>0.9</td>
<td>0.4, 1.8</td>
</tr>
<tr>
<td><strong>P</strong>&lt;sup&gt;trend&lt;/sup&gt;</td>
<td>0.59</td>
<td>0.42</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for age, sex, and other beverage types.
<sup>b</sup> 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 synthetases 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.

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Conflict of interest: none declared.

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