Author’s response to reviews

Title: Alcoholic cirrhosis in Denmark - population-based incidence, prevalence, and hospitalization rates between 1988 and 2005: a descriptive cohort study

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Author’s response to reviews: see over
Dear Editor,

We thank the reviewers for their insightful comments. We have done our best to address them here and in the revised manuscript. Changes in the manuscript are in red font. We hope that the responses presented below and the revised manuscript meet your expectations. We appreciate the opportunity to submit a revised manuscript.

Yours sincerely,

Peter Jepsen, MD
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Reviewer #1

Major compulsory revisions

1. Do these age-specific trends mean that alcohol-harm in general has developed differently across age groups, do other harm indicators confirm the pattern or are they only relevant to alcoholic cirrhosis?

Please see our response to comment #3.

2. What are the possible explanations for these age-specific differences, for instance the decline in younger age groups? A higher ambition with respect to explaining the results are needed in terms of possible cohort effects (is it really a cohort study as the title suggests?), consequences of policy changes etc.

Please see our response to comment #3.

3. I also miss a more comprehensive and detailed description of the survey findings the authors refer to that show a similar age-specific pattern with respect to self-reported alcohol consumption. When were they conducted and in what way too the results match (or not match) the cirrhosis results?

Comments #1, 2, and 3 are best addressed collectively: The study is a cohort study in several meanings of the word [Last JM. A dictionary of epidemiology. 4th ed. New York: Oxford University Press 2001]. The Danish population may be considered a cohort [Frank L. When an entire country is a cohort. Science 2000;287:2398-9], and the incidence rate of alcoholic cirrhosis is based on that cohort. A second cohort, consisting of the alcoholic cirrhosis patients in the Danish population, was followed from diagnosis to obtain hospitalization and
prevalence rates. However, we agree with the reviewer that the analyses and discussion did not consider birth cohorts in sufficient detail. Distinguishing age, period, and cohort effects is challenging, and no statistical analyses can accurately do so [Glenn ND. Distinguishing age, period, and cohort effects. Handbook of the life course. Hingham, MA, USA: Kluwer Academic Publishers 2003:465-76]. That said, we gained new insight when we tabulated our data in a way that made it possible to see age, birth, and cohort effects simultaneously. This table is discussed below and included in the revised manuscript:

Table 2 Incidence rates of alcoholic cirrhosis, per 1,000,000 population, for men (top) and women (bottom) by age and calendar year. Age- and calendar year-intervals are chosen so that a birth cohort can be followed through time by going diagonally down and to the right. For example, those who were aged 25-29 years in 1986-1990 were born between 1957 and 1965, with the majority born in 1961. The incidence rates in bold letters are all for that birth cohort.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
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<th></th>
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</thead>
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<tr>
<td>1986-90</td>
<td>0</td>
<td>18</td>
<td>79</td>
<td>203</td>
<td>304</td>
<td>432</td>
<td>493</td>
<td>561</td>
<td>483</td>
<td>389</td>
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<tr>
<td>1991-95</td>
<td>0</td>
<td>15</td>
<td>74</td>
<td>230</td>
<td>352</td>
<td>445</td>
<td>583</td>
<td>629</td>
<td>575</td>
<td>464</td>
<td>316</td>
<td>182</td>
</tr>
<tr>
<td>1996-00</td>
<td>0</td>
<td>12</td>
<td>47</td>
<td>162</td>
<td>392</td>
<td>536</td>
<td>664</td>
<td>805</td>
<td>807</td>
<td>590</td>
<td>453</td>
<td>245</td>
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<tr>
<td>2001-05</td>
<td>1</td>
<td>5</td>
<td>32</td>
<td>123</td>
<td>287</td>
<td>592</td>
<td>726</td>
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<td>1986*</td>
<td>11</td>
<td>44</td>
<td>102</td>
<td>142</td>
<td>191</td>
<td>210</td>
<td>265</td>
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<tr>
<td></td>
<td>1991-95</td>
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<td>230</td>
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<td>10</td>
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<td>314</td>
<td>384</td>
<td>370</td>
<td>277</td>
<td>163</td>
</tr>
</tbody>
</table>

* Data for 1986 and 1987 were not used.
The table indicates that the 45-49 years age category follows the same increasing time trend as the 50-54 years age category, and that the incidence rate is only decreasing among younger patients. Therefore, in the revised manuscript, we have changed the age categories to 0-44 years, 45-64 years, and 65 years or older [for example, page 5, line 1 in the revised manuscript].

The table also shows that men and women who were aged 25-29 years in 1986-1990, i.e. born in 1957-1965 (highlighted with bold numbers), had a lower incidence rate of alcoholic cirrhosis than earlier birth cohorts at all ages. Furthermore, later birth cohorts had progressively lower incidence rates [page 7, line 9 in the revised manuscript].

The reasons for the increase in alcoholic cirrhosis incidence among older men and women are not clear. We note, however, that the birth cohort from 1917-25 (who were aged 65-69 years in 1986-90) and earlier birth cohorts may have had a lower incidence rate than later birth cohorts [page 7, line 11 in the revised manuscript].

Together, our findings forecast a continued increase in alcoholic cirrhosis incidence in the elderly population (65+) over the next one or two decades. At the same time, the incidence rate will continue to decrease in the younger population, and the decreasing trend will eventually spread to older age groups [page 11, line 12 in the revised manuscript].

Our findings are consistent with national statistics and recent surveys. There was a considerable increase in per adult (>14 years) alcohol consumption between 1965 and 1975, from 7 to 12 liters, and it is likely that those born between 1925 and 1950 were primarily responsible for this increase. The per adult consumption has been nearly stable since 1975, and this is probably explained by a continued high consumption in the 1925-1950 birth cohort combined with a relatively low consumption in the birth cohorts from 1960 and later [page 10, line 23 in the revised manuscript].
The study by Gerdes et al. concerned men and women aged 30, 40, 50, or 60 years surveyed in 1982-84, 1986-87, and 1991-92 [Gerdes LU, et al. Trends in lifestyle coronary risk factors in the Danish MONICA population 1982-1992. Public Health. 2002;116:81-8]. The 6695 participants were asked about their average weekly alcohol consumption, and consumption was trichotomized as no/low/high, with high alcohol consumption defined as more than 21 units per week for men and 14 for women. Among both men and women, alcohol consumption decreased among 30-year-olds, i.e. the 1961-62 birth cohort consumed less alcohol than the 1952-54 birth cohort. Most of this decrease occurred between the 1986-87 and the 1991-92 surveys, i.e. the 1961-62 birth cohort consumed less alcohol than the 1956-57. This is consistent with our findings. Changes were small and not statistically significant among older men and women, i.e. there were no apparent changes in alcohol consumption between the 1922-24 birth cohort and the 1951-52 birth cohort. This is also consistent with our findings [page 11, line 2 in the revised manuscript].

In the study by Såbye-Hansen et al., 4016 men and 4179 women aged 15-79 years were surveyed in 1992 about alcohol intake the previous day [Såbye-Hansen H, et al. Changes in the drinking pattern in Denmark from 1979 to 1992. In Danish with English abstract. Ugeskr Laeger 1998;160:7118-21]. These results were compared with those from a similar survey conducted in 1979. Among men and women younger than 40 years, there was a statistically significant decrease in the proportion who reported alcohol consumption on the previous day, i.e. the 1952-77 birth cohort consumed less alcohol than the 1939-64 birth cohort. Furthermore, the proportion who reported alcohol consumption increased among men and women over the age of 40 years, i.e. the 1913-1952 birth cohort consumed more alcohol than the 1900-1939 birth cohort. These findings are consistent with ours [page 11, line 4 in the revised manuscript].
In the study by Bjørk et al., 11,754 men and women aged 50 years or older were asked about their alcohol intake on the previous working day in 1987, 1994, 2000, and 2003 [Bjørk C, et al. Alcohol consumption by middle-aged and elderly Danes from 1987 to 2003. In Danish with English abstract. Ugeskr Laeger 2006;168:3317-21]. The authors found a statistically significantly higher alcohol intake for birth cohorts before 1953 than for birth cohorts before 1937. This is consistent with our findings. They also showed that alcohol consumption decreased among men and women aged 16-49 years, i.e. the 1938-1971 birth cohort drank more than the 1954-1987 birth cohort. This is also consistent with our findings [page 11, line 5 in the revised manuscript].

Why, then, do those who were born around 1960 or later consume less alcohol than their parents did? It is conceivable that alcohol has simply been replaced by other means of intoxication. Alternatively, sensible drinking campaigns, of which there have been many in recent decades, may have had an effect on the young, but not on the old who have become habitual alcohol consumers as a result of social and cultural changes during their lifetime [Bjørk C, Vinther-Larsen M, Thygesen LC, Johansen D, Grønbæk MN. Alcohol consumption by middle-aged and elderly Danes from 1987 to 2003. In Danish with English abstract. Ugeskr Laeger 2006;168:3317-21]. This is supported by an increase in the proportion of Danes who drank wine with dinner from 1979 to 1992 [Såbye-Hansen H, Grønbæk MN, Hardt F, Becker PU, Sørensen HT, Vilstrup H. Changes in the drinking pattern in Denmark from 1979 to 1992. In Danish with English abstract. Ugeskr Laeger 1998;160:7118-21] [page 11, line 9 in the revised manuscript].
Minor Essential Revisions

4. *The difference between incidence, prevalence and hospitalisation rates needs to be more clearly explained.*

In the original manuscript, we wrote the following definitions on pages 4-5: “The incidence rate was defined and computed as the number of patients with a first-time hospital discharge diagnosis of alcoholic cirrhosis in a particular year divided by the total number of Danish citizens at the beginning of that year.” “The prevalence rate was defined and computed as the number of patients in the cirrhosis cohort at the end of a particular year divided by the number of Danish citizens in the beginning of that year.” “The hospitalization rate was defined and computed as the total number of inpatient admissions for the members of the cirrhosis cohort in a particular year divided by the number of Danish citizens recorded at the beginning of that year.” We agree that these definitions do not describe what the rates *mean*, and we have added a short explanatory sentence to each definition [page 4, line 19, page 5, line 15, and page 5, line 19 in the revised manuscript].

5. *The information presented in the graphs are very difficult to follow and I suggest that they must be revised.*

We have attempted to make it easier to perceive the pieces of information the figure conveys. In the absence of specific requests, we have not changed the figure’s design. We still like to show time trends in incidence, hospitalization, and prevalence rates in the same figure, but have made the following changes:

a. Increased the spacing between the panels to make it easier to distinguish labels on the left-hand vertical axes from those on the right-hand vertical axes.
b. Changed the right-hand vertical axes to minimize overlap between incidence rates and prevalence/hospitalization rates.

c. The incidence rates for, say, men aged 45-64 years is a series of dots, one per year. The dot for 1995 represents the 'average' incidence rate for 1995. We did not examine whether the incidence rate changed during 1995. In the original manuscript version, we connected the 1995-dot with the 1996-dot by a horizontal line throughout 1995 followed by a vertical step. Although this is the correct way to display the information, the resulting stair-like plot increased the overlap between the incidence, prevalence, and hospitalization rates. In the revised version, we connect the 1995- and 1996-dots by a straight line to facilitate the visual interpretation.
Reviewer #2

Major Compulsory Revisions

1. *It appears that their definition of alcoholic cirrhosis requires at least an initial admission to a hospital with a diagnosis of alcoholic cirrhosis. However, there are certainly cirrhotics with well compensated liver disease without portal hypertension that do not require hospitalization. Cirrhosis is a histological diagnosis, and many patients do not develop symptoms of clinical portal hypertension for years. So, based on their ascertainment algorithm for identifying Danish citizens with alcoholic cirrhosis, they are likely not capturing all cases of alcoholic cirrhosis who are only being cared for as outpatients and have not been hospitalized. At the very least, their incidence rates reflect a lag time between onset of histological cirrhosis and appearance of clinical manifestations that require HOSPITALIZATION. Thus, either the definition of cirrhosis (i.e. decompensated cirrhosis requiring hospitalization) needs to be modified or the authors need to clearly clarify their assumptions that all alcoholic cirrhosis cases will be eventually hospitalized (which is not necessarily true). It would be preferable to combine hospital discharge data with the outpatient registry data which would include cirrhotics who were never hospitalized. It appears that data from outpatient and emergency room visits may have been included in the analysis but it is unclear how. Or if it is standard practice in Denmark to admit to a hospital every new diagnosis of alcoholic cirrhosis for evaluation, then that needs to be stated.*

The reviewer is correct that we identified only hospitalized cirrhosis patients, and we may consequently underestimate the true incidence rate. This has been emphasized [page 9, line 1 in the revised manuscript]. Unfortunately, the criteria for *inpatient* admission of a cirrhosis patient are unclear and may have changed over time. Decompensated cirrhosis, i.e. with ascites or variceal bleeding [D'Amico G, et al. Natural history and prognostic indicators of
survival in cirrhosis: A systematic review of 118 studies. J Hepatol 2006;44:217-31], is not necessary for admission, and the diagnosis is more often based on a combination of clinical findings, blood tests, and ultrasound findings than on liver biopsy, and it can therefore be made in the outpatient setting. We agree, however, that there is a lag time between histological onset of cirrhosis and hospital discharge diagnosis, and this lag time may be shorter when outpatient data are available. In our study, outpatient data were available – and used – from around 1995 [page 3, line 17 in the original manuscript], and we examined “whether the gradual inclusion of data from outpatient and emergency room visits to the National Patient Registry affected incidence rates” [page 5, line 9 in the original manuscript]. We found that “incidence trends were not affected by restricting our data to data from inpatient hospitalizations” [page 7, line 11 in the original manuscript], but we concur that this does not fully address the issue. It remains correct that the time trends would have been essentially the same if we had not included data from outpatient and emergency room visits as they became available (i.e., in the figure below, the time trend in the dashed line is the same as that in the solid line), but they did contribute to the sudden incidence rate increase around 1994. This has been clarified [page 9, line 23 in the revised manuscript].

![Graph showing incidence rates over time](image-url)
The vertical distance between the solid and the dashed lines is approximately 20 per 1,000,000 population, so it appears that the proportion of Danish cirrhosis patients seen as outpatients only remains constant at around 10 percent. This has been added to the revised manuscript [page 7, line 15].

2. The authors are correct in stating that a 32% increase in incidence in one year followed by stabilization of rates is implausible. This is very likely to be due to the change from ICD8 to ICD10 coding given that the rate increase occurred at the same time as the coding change. Though there may be only one unambiguous diagnosis code for alcoholic cirrhosis, perhaps there were peripheral changes with other competing liver-related codes or coding processes that resulted in an increase of diagnoses for alcoholic cirrhosis. I think more emphasize needs to be placed on the shift of ICD coding because of the striking temporal association with the rise in incidence.

We agree that the change in ICD coding must have contributed, although the exact mechanism remains unclear. We have emphasized this point in the revised manuscript [page 10, line 5].

3. It is difficult for the reader to assess what impact the increase in average number of 1.3 to 1.5 hospitalizations per patient for men and 1.1 to 1.2 hospitalizations per patient for women has on the Danish healthcare system. The authors’ point could be more clearly conveyed if they also presented data on trends in the total number of hospitalizations throughout the country, which truly reflects the economic burden on the health system.

The total number of inpatient hospitalizations for patients with alcoholic cirrhosis (per
1,000,000 population) is the definition of the hospitalization rate. Thus, if we understand the reviewer correctly, the requested data can be found in Table 1 and in Figure 1.

**Discretionary Revisions**

4. *If available, it would be helpful to include time trends in in-hospital mortality data for patients admitted with the primary diagnosis of alcoholic cirrhosis. This would allow an assessment of whether the severity of disease has increased or decreased over time, since a rise in hospitalizations may reflect a shift in practice patterns to admit less ill patients.*

We agree that it would be interesting to investigate such a shift in practice, and we have tried to implement the reviewer’s suggestion. We identified patients with a first primary diagnosis of cirrhosis from an inpatient hospitalization in 1988 or later, and we used logistic regression to examine the effect of calendar year with adjustment for changes in age- and gender-composition of cirrhosis patients over time. We found that the odds of dying during the first admission decreased by a factor of 0.993 (95% confidence interval = 0.984 to 1.001, p = 0.085) per year. This is consistent with the suggestion that inpatients with cirrhosis are less ill now than they used to be. However, we believe that a strong alternative explanation is that treatment has improved, as reported by e.g. a Swedish study [Stokkeland K, et al. Improved prognosis for patients hospitalized with esophageal varices in Sweden 1969-2002. Hepatology 2006;43:500-5]. Therefore, a change in practice towards admitting less ill patients could be better examined with clinical data, which we do not have access to. As it is, we prefer not to include this analysis of mortality in the present manuscript because it is outside the manuscript’s scope and raises more questions than it answers. Therefore, we will address time trends in the mortality of cirrhosis patients in a separate study.