Epidemiology of Alcoholic Liver Disease in Denmark 2006–2011: A Population-Based Study

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Abstract

Aims: To describe incidence, prevalence, hospitalization rates and survival for alcoholic liver disease (ALD) in Denmark 2006–2011.


Results: In 2006–2011, the overall standardized ALD incidence decreased from 343 to 311 per 1,000,000 population per year. ALD incidence increased among women aged 65 years or older, but decreased in younger persons and men. Persons born in 1950–1959 had higher age-specific incidence than earlier and later birth cohorts. The prevalence (0.2% of the Danish adult population) and hospitalization rate were constant. The 1- and 5-year survival were 43 and 70%, respectively.

Conclusion: In Denmark, persons born in 1950–1959 have had the highest age-specific incidence. The overall ALD incidence has been decreasing (along with per capita consumption). Despite increases in affordability during the study period, Denmark did not experience the increase in ALD seen, for example, in the UK. It is possible that this is due to the greater impact of government recommendations on safer drinking in Denmark than the UK.

INTRODUCTION

Alcoholic liver disease (ALD) comprises alcoholic steatosis, alcoholic hepatitis and alcoholic cirrhosis (Lancet, 1981). Per capita alcohol consumption is a strong predictor of a country’s incidence and mortality rates of alcoholic liver cirrhosis (Ramstedt, 2001), and self-reported alcohol consumption predicts an individual’s risk of developing liver disease (Becker et al., 1996). It is estimated that 860,000 Danish residents, corresponding to 1/6 of the Danish population, consume alcohol in amounts that put them at risk of developing liver disease (Hansen et al., 2011). We have previously described Danish incidence rates of alcoholic liver cirrhosis 1988–2005 and alcoholic hepatitis 1999–2008 (Jepsen et al., 2008; Sandahl et al., 2011). Both studies showed an increasing incidence, but also predicted a future decrease because the incidence decreased among persons born after 1960. The two factors known to affect alcohol consumption the most, pricing and availability, have changed in recent years (Grittner et al., 2009; Bloomfield et al., 2010), and data on the current and future burden of ALD are scarce. We aimed to provide information on ALD incidence, prevalence,
hospitalizations, and patient survival in Denmark 2006–2011, and in order to predict future incidence rates we also computed birth cohort-specific ALD incidence. Such data are necessary to plan and evaluate preventive measures and to monitor the public health.

METHODS

Setting and data sources
We performed this registry-based historical descriptive study in Denmark which has 5.6 million inhabitants. All Danish residents are provided universal, tax-supported access to general practitioners and hospitals. The Danish National Patient Registry (NPR) is a nationwide registry covering admissions to non-psychiatric hospitals since 1977 and outpatient and emergency room visits since 1995. Data include relevant dates and discharge diagnoses coded in accordance with the International Classification of Diseases, edition 10 (ICD-10) from 1994 and the ICD-8 before that (Andersen et al., 1999). The Danish Central Office of Civil Registration continuously monitors Danish residents' vital status including dates of emigration or death. All residents in Denmark are issued a unique personal identifier at birth or immigration, and it enables linkage of individual-level data between the NPR and the civil registration system (Pedersen et al., 2006).

Study population
We identified all patients with a first-time diagnosis of alcoholic cirrhosis (ICD-8: 571.09, ICD-10: DK70.2, DK70.3, and DK70.4), alcoholic hepatitis (ICD-10: DK70.1), alcoholic steatosis (ICD-8: 571.10, ICD-10: DK70.0) or unspecified alcoholic liver disease (ICD-10: DK70.9) from 1 January 1977 to 31 December 2011 in the NPR to avoid mixing incident and prevalent patients. The date of inclusion was the admission date of the first hospitalization resulting in one of these diagnoses. If patients received more than one diagnosis at inclusion, the diagnoses were ranked in this order: cirrhosis > hepatitis > steatosis > unspecified, and patients were assigned the diagnosis with the highest rank.

Statistical analysis
The incidence rate describes the rate at which Danish residents are diagnosed with alcoholic liver disease. It was computed as the number of patients with a first-time diagnosis of ALD in a specific year divided by the number of residents in Denmark on 1 January of the same year. These incidence rates were standardized to the Danish population on 1 January 2011. We calculated standardized overall, gender- and age-specific (15–44 years, 45–64 years, and 65 years or older) incidence in 2006–2011 with corresponding 95% confidence intervals. Further, we used Poisson regression to compute the ALD incidence rate ratio (IRRs) for 2011 vs. 2006 adjusted for age and gender differences. We included calendar year as an indicator variable (2006 coded as ‘0’, 2011 coded as ‘1’). In addition, we repeated these analyses and restricted them to patients with cirrhosis.

Finally, we divided all patients diagnosed with ALD after 1 January 1980 into cohorts by birth year in 5-year intervals. For each birth cohort from 1930–1934 through 1970–1974 we computed age-specific incidence rates. We did not have access to birth cohort-specific demographics for the Danish population; instead, the denominator in this analysis was the Danish population on 1 January the year each birth cohort entered the relevant age category. Hence, the incidence rate for the 1960–1964 birth cohort at age 40–44 years was the number of ALD patients aged 40–44 years born in 1960–1964 divided by the Danish population aged 40–44 years in the calendar years 2000–2004. Further, we repeated these analyses separately for men and women, for cirrhosis patients, for cirrhosis patients diagnosed after 1994, for alcoholic hepatitis patients, and for patients diagnosed with ALD at inpatient hospitalizations.

The prevalence describes the proportion of the Danish population aged 15 years or more with a hospital diagnosis of ALD. It refers to a specific point in time, and we chose January 1 of the years 2006 through 2011. To compute the prevalence we used the number of ALD patients under observation in our cohort of ALD patients on January 1 of a specific year divided by the population size on the same date. We had to use data dating back to the inception of the NPR in 1977 in order to identify everyone who had been diagnosed with ALD and was still alive on 1 January 2006. Again, we standardized these prevalence estimates to the Danish population on 1 January 2011 using direct standardization, and we also repeated the analyses restricting them to patients with cirrhosis.

The hospitalization rate describes the number of inpatient admissions for patients with ALD in a given year divided by the total number of Danish residents at the beginning of the same year. Also these rates were standardized to the Danish population on 1 January 2011. Transfers between hospital departments were not counted as new admissions. The number of inpatient hospitalizations per patient in a given year was obtained by dividing the standardized hospitalization rate by the prevalence of ALD in the same year. The number of days each ALD patient was admitted per year was computed as the total number of days all ALD patients spent in hospital each year divided by the number of prevalent ALD patients at the beginning of the same year.

The Kaplan–Meier method was used to estimate overall 1- and 5-year survival from ALD diagnosis. Patients were included from 1 January 2006 until 31 December 2011, and follow-up ended on 31 December 2011. We used Cox regression to control for confounding by age, gender and diagnosis: alcoholic cirrhosis, alcoholic hepatitis, alcoholic steatosis (reference category) and unspecified ALD. All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas) and R version 2.14 (R, 2013).

Beginning in 1994, the National Institute of Public Health has conducted surveys of the Danish population every 5 years to determine the prevalence of harmful alcohol intake (men >21 standard alcohol units (SAU) per week, women >14 SAU per week, 1 SAU = 12 g ethanol) (NIPH, 2010), and these data are publicly available (NIPH, 2014). To ease the interpretation of our analyses, we extracted these data for 1994, 2000, 2005 and 2010 by gender and age category.

RESULTS

A total of 10,835 Danish residents were diagnosed with ALD between 1 January 2006 and 31 December 2011. The majority (68%) were men, the median age was 58 years and half of patients were aged between 51 and 65 years. The distribution of diagnoses did not change during the study period: 7296 (67%) had alcoholic cirrhosis, 789 (7%) alcoholic hepatitis, 1452 (14%) alcoholic steatosis and 1298 (12%) unspecified ALD.

Incidence
In 2006–2011, men’s ALD incidence rate decreased among those younger than 65 years and was constant among those aged 65 years or older. Women’s ALD incidence, by contrast, decreased only in the
youngest age group (15–44 years) and increased in the oldest (≥65 years). The net result was an overall reduction in ALD incidence driven by a decreasing incidence among those younger than 65 years (Figs. 1 and 2, Table 1). We found similar time trends in incidence when we restricted the analyses to cirrhosis diagnoses. The 1950–1959 birth cohorts had higher age-specific incidence rates of ALD than earlier and later birth cohorts (Fig. 3). This pattern was unaltered when we analysed men and women separately, restricted our analyses to cirrhosis patients, to cirrhosis patients diagnosed after 1994, to alcoholic hepatitis patients, or to patients diagnosed at inpatient hospitalizations.

Prevalence
On 1 January 2006, 11,482 Danish residents had been diagnosed with ALD, corresponding to a standardized prevalence of 0.217% (95% CI: 0.216–0.220) of the adult population (15 years or older). The prevalence remained stable through 2011 and was about two times higher for men (0.288% [95% CI: 0.285–0.291]) than for women (0.152% [95% CI: 0.150–0.154]) (Supplementary Fig. SA). We found a similarly stable prevalence when we restricted the analysis to cirrhosis diagnoses (0.109% [95% CI: 0.112–0.106]).

Hospitalizations
The 11,482 Danish residents with ALD alive on 1 January 2006 accumulated 13,678 inpatient hospitalizations in 2006, equalling 2580 (95% CI: 2573–2624) inpatient hospitalizations per 1,000,000 population and 1.19 hospitalizations per ALD patient. The number of hospitalizations per patient increased slightly during the study period to 1.26 per year in 2011 (Supplementary Fig. SB). Men were admitted 1.29 times per year compared with women’s 1.15 times, and the annual number of days spent in hospital per ALD patient decreased from 8.8 in 2006 to 7.9 in 2011.

Survival
The overall 1- and 5-year survival from ALD diagnosis was 70% (CI 95%; 69–71%) and 43% (95% CI: 42–45%), respectively. Men had poorer survival than women, and patients with alcoholic cirrhosis or alcoholic hepatitis had poorer survival than patients with alcoholic steatosis (Fig. 4 and Table 2).

Harmful alcohol intake
The proportion of Danes with a harmful alcohol intake peaked in 2005. Between 2005 and 2010 it continued to rise among those aged 16–24 years, but fell in the other age groups (Fig. 5).

DISCUSSION
This nationwide population-based study showed that the ALD incidence in Denmark decreased between 2006 and 2011. This overall reduction was the result of a decreasing incidence in the population younger than 65 years, and an increasing incidence in the population aged 65 years or older. The 1950–1959 birth cohorts were more likely to develop ALD than earlier or later birth cohorts. The ALD prevalence was stable at 0.22 % of the general population, and the number of hospitalizations per ALD patient per year was also fairly stable. The survival of ALD patients diagnosed in 2006–2011 was poor, most so for those with cirrhosis.

The strengths of our study are its nationwide setting and population-based design with complete follow-up. A possible limitation is the quality of the data sources. Becker et al. and Vestberg et al. found that presence of cirrhosis was confirmed by biopsy or clinical evaluation in 92 and 86% of patients with a diagnosis code for alcoholic liver cirrhosis in the Danish National Patient Registry (Becker et al., 1996; Vestberg et al., 1997). We also have confidence in the validity of the alcoholic aetiology, because according to Danish clinical practice it requires exclusion of other causes of liver disease and a verified history of harmful alcohol intake. Moreover, the prevalence of hepatitis B and C in Denmark is less than 0.5% (Christensen et al., 2012; Hansen et al., 2013). The transition to ICD-10 in 1994 and the inclusion of emergency room and outpatient visits to the NPR in 1995 could have affected our birth cohort analysis, but our analyses
contest this notion: the transition to ICD-10 could not possibly explain the consistently higher age-specific incidence rates for the 1950–1959 birth cohort; in 1994 this cohort was no older than 35–39 years. For example, in the 45–49 year age group, the incidence rate was 494 per million population for the 1945–1949 birth cohort, 616 per million population for the 1949 birth cohort, and 476 per million population for the 1960–1964 birth cohort.

Our findings of a decreasing overall incidence of ALD in Denmark confirm predictions in previous Danish studies (Jepsen et al., 2008; Sandahl et al., 2011), and contrasts with reports from the UK and Eastern Europe (Leon and McCambridge, 2006; Ramstedt, 2007; Fleming et al., 2008; Ensleie et al., 2009; Ratib et al., 2014). Annual per capita alcohol consumption in Denmark rose from the mid-1960s to the mid-1980s and has decreased slightly since then (Denmark Statistics, 2013). Several studies have demonstrated that alcohol intake varies by birth cohort (Rosen and Haglund, 2006; Keyes et al., 2011; Kerr et al., 2013), and a Danish study based on the surveys conducted by the National Institute of Public Health showed that the 1940–1955 birth cohorts had a higher alcohol intake than earlier birth cohorts (Bjørk et al., 2008). Thus, it appears that the ‘baby boomer generation’ born in 1950–1959 has the highest alcohol consumption, and we believe that they now suffer the consequences by developing liver disease around age 60 years, the age at which the incidence of alcoholic liver disease peaks. Our belief is reinforced by the strong correlation between per capita alcohol consumption and cirrhosis incidence in European countries (Ramstedt, 2001). But, in contrast to the expectations for the UK (Fleming et al., 2008; Bhal et al., 2013; Ratib et al., 2014), we predict that the total incidence of ALD will decrease further in the years to come owing to the decreasing incidence in the birth cohorts born after 1960 and the decreasing prevalence of harmful alcohol intake.

There is strong evidence for a relation between alcohol pricing, alcohol consumption and alcohol-related deaths at the population

| Table 1. Standardized incidence rate and incidence rate ratios by gender and age category for 2011 vs. 2006 with 95% confidence intervals |
|----------------|----------------|----------------|
| Age category  | SIR 2006       | SIR 2011       | IRR 2011 vs. 2006* |
| Overall       | 343 (95% CI: 327–359) | 311 (95% CI: 297–326) | 0.91 (95% CI: 0.83–0.97) |
| 15–44         | 102 (95% CI: 89–115)  | 71 (95% CI: 60–82)  | 0.69 (95% CI: 0.57–0.86) |
| 45–64         | 831 (95% CI: 784–878) | 741 (95% CI: 697–784) | 0.90 (95% CI: 0.83–0.97) |
| ≥65           | 514 (95% CI: 461–566) | 545 (95% CI: 497–594) | 1.07 (95% CI: 0.93–1.22) |
| Men           | 481 (95% CI: 454–508) | 425 (95% CI: 401–450) | 0.88 (95% CI: 0.81–0.95) |
| 15–44         | 147 (95% CI: 125–170) | 105 (95% CI: 86–125) | 0.72 (95% CI: 0.56–0.91) |
| 45–64         | 1135 (95% CI: 1058–1212) | 992 (95% CI: 920–1063) | 0.87 (95% CI: 0.79–0.96) |
| ≥65           | 764 (95% CI: 671–857) | 761 (95% CI: 677–844) | 1.00 (95% CI: 0.85–1.18) |
| Women         | 209 (95% CI: 192–227) | 200 (95% CI: 184–217) | 0.97 (95% CI: 0.86–1.09) |
| <45           | 55 (95% CI: 41–69) | 36 (95% CI: 24–47) | 0.65 (95% CI: 0.43–0.98) |
| 45–64         | 525 (95% CI: 473–578) | 490 (95% CI: 440–540) | 0.94 (95% CI: 0.82–1.09) |
| ≥65           | 297 (95% CI: 243–352) | 353 (95% CI: 298–407) | 1.20 (95% CI: 0.94–1.51) |

*Adjusted for age and gender.
Table 2. Survival of Danish patients diagnosed with alcoholic liver disease in 2006–2011, by gender and ALD diagnosis with 95% confidence intervals

<table>
<thead>
<tr>
<th>Gender</th>
<th>1-year survival</th>
<th>5-year survival</th>
<th>Adjusted hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>68.6% (67.6–69.7%)</td>
<td>41.3% (39.7–42.9%)</td>
<td>1.17 (1.10–1.25)</td>
</tr>
<tr>
<td>Women</td>
<td>72.7% (71.1–74.1%)</td>
<td>47.5% (45.2–49.9%)</td>
<td>1.00b</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
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</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>63.7% (62.6–64.9%)</td>
<td>35.4% (33.8–37.1%)</td>
<td>2.34 (2.18–2.52)</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>73.4% (70.1–76.4%)</td>
<td>52.5% (47.8–57.1%)</td>
<td>2.35 (1.99–2.76)</td>
</tr>
<tr>
<td>Unspecified ALD</td>
<td>79.3% (76.9–81.4%)</td>
<td>53.3% (49.5–56.8%)</td>
<td>1.93 (1.66–2.34)</td>
</tr>
<tr>
<td>Alcoholic steatosis</td>
<td>90.9% (89.2–92.3%)</td>
<td>69.5% (65.9–72.8%)</td>
<td>1.00b</td>
</tr>
</tbody>
</table>

bReference category.
aAdjusted for age, gender, and ALD diagnosis.

Fig. 5. Prevalence of harmful alcohol intake in the Danish population 1994–2010 by age category and gender (data from the National Institute of Public Health).

level (Chisholm et al., 2006; Zhao et al., 2013). Since the 1980s, alcohol has become increasingly affordable in the UK and the numbers of cirrhosis deaths have gone up (Sheron et al., 2008; Record and Day, 2009). The taxation on alcohol in Denmark was reduced in 2003 and again in 2005, and at the same time restrictions on alcohol sales after 8 p.m. and alcohol imports were lifted. There was great concern that alcohol consumption would increase, but it did not (Grittner et al., 2008; Record and Day, 2008). The divergent consequences of increased affordability and availability of alcohol between Denmark and the UK may be explained by differences in recognition of sensible drinking limits: In 1990, the Danish National Board of Health adopted recommendations for sensible drinking limits from the UK Royal Colleges of Physicians (RCP, 1987). These recommendations have been advocated aggressively in Denmark resulting in higher public awareness than in the UK (Gronbaek et al., 2001; Gill and O’May, 2006, 2007). A direct comparison of the public attention to the sensible drinking message in Denmark and the UK is impeded by the difference in survey design and timing, but we speculate that the lower awareness in the UK may arise because the British Government promoted different drinking limits than the Royal Colleges of Physicians, thereby stirring up confusion rather than clarifying the message (Edwards, 1996). Lobbying and advertising by the alcohol industry may also have been more successful in the UK than in Denmark.

The survival of patients with ALD was poor: only about 45% of patients survived 5 years after their diagnosis and men had worse prognosis than women, which mirrors Swedish studies on ALD prognosis (Stokkeland et al., 2006, 2010). Alcoholic hepatitis patients’ survival was superior to cirrhosis patients’, most likely because patients with alcoholic hepatitis superimposed on cirrhosis were included as cirrhosis patients, not hepatitis patients. Still, this finding conflicts with previous studies (Orrego et al., 1987; Bouchier et al., 1992), but these earlier studies were based on small clinic-based patient series with losses to follow-up, and they defined ALD diagnosis by historical rather than clinical criteria.

In conclusion, between 2006 and 2011 the ALD incidence decreased in persons younger than 65 years and in men, and these changes resulted in a decreasing overall incidence. Moreover, the ‘baby boomer generation’ born in 1950–1959 had a higher incidence of ALD than earlier and later birth cohorts. We expect the incidence of ALD to decrease further owing to the decreasing incidence in the population born after 1960.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Alcohol and Alcoholism online.

CONFLICT OF INTEREST STATEMENT


REFERENCES


RCP Royal College of Physicians. The medical consequences of alcohol abuse, a great and growing evil. 1987. Tavistock Publications Ltd.


